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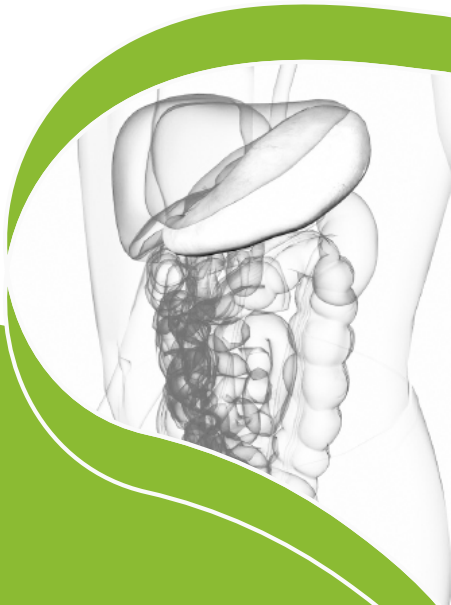
ANDALUSIAN JOURNAL OF DIGESTIVE PATHOLOGY



Official Body of Sociedad Andaluza de Patología Digestiva

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ANDALUSIAN JOURNAL OF DIGESTIVE PATHOLOGY

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1. RAPD Objectives and characteristics: The Revista Andaluza de Patología Digestiva is the official publication of the Andalusian Society of Digestive Pathology (SAPD), which since 2007 has been published in electronic format only, under the name RAPD Online. Its purpose is to disseminate all epidemiological, clinical, basic and sociological aspects of digestive diseases, through the contributions sent to the journal from Andalusia and from the entire scientific community. The official language for the publication of this journal is Spanish, but some contributions may be accepted in the author's original language in English, French or Italian. RAPD Online is published bimonthly, with one of the issues being specially dedicated to the Annual Meeting of the SAPD and the Editorial Board deciding to reserve one or more issues per year for the monographic development of a topic related to the speciality.

All submitted contributions must be original and not be simultaneously under review for publication in another journal. The publication of abstracts or posters is not considered duplicate publication. Manuscripts will be evaluated by expert reviewers, appointed by the editorial board, before being accepted for publication, in a process that will take less than 30 days.

2. RAPD Contents: *regular numbers of RAPD Online include defined sections such as:*

- *Original articles on clinical or basic research.*
- *Thematic reviews on specific aspects of Gastroenterology.*
- *Consensus documents.*
- *Clinical cases.*
- *Clinical cases with videos or Videoforum.*
- *Images of the month.*
- *News and updates on gastroenterology and hepatology.*
- *Letters to the Editor.*

Other contributions that are considered of interest by the Editorial Board, relating to different aspects of clinical practice in the recent past, biographical comments, or other contents of a cultural nature, or related to scientific activities in any territorial area, will be inserted in RAPD Online in sections designed specifically for this purpose.

3.Submission of manuscripts: *The preferred way to submit manuscripts is through the SAPD website (https://www.sapd. es), by accessing the RAPD Online page and clicking on the "Submit an original" button located on the same access page to the journal. This will take you to the Manuscript Centre, from where you will be able to send manuscripts and all the required documentation. To use this tool you must be previously registered, access requires a username and password. If you are a member of the SAPD, you can use your usual username. If you are not a member, you can request a username for access to the Manuscript Centre using the form on the website. You can write to sulime@sulime.net or RAPDonline@sapd.es, for the solution of any problem in the submission of manuscripts.*

4. Writing standard for manuscripts: *monographic numbers, thematic reviews, updates and annotated articles will be commissioned by the Editorial Board, but the submission of any of these contributions at the request of an author will be considered by the RAPD Online Management and evaluated with great interest for inclusion in the journal.*

All manuscripts will be subject to specific rules, depending on the type of contribution, and to common ethical and legal standards.

A) Specific standard for manuscripts writing

They refer to the recommended length and structure of each type of manuscript. As a basic unit of length for the text, in any of the contributions, a page of 30-31 lines, spaced 1.5 lines apart, with a font size of 12, with 75-80 characters without spaces per line and a total of 400-450 words per page is considered. Texts should be sent spell-checked and in editable format in all their applications (main text, figures, legends or figure captions, tables, graphs, drawings).

Originals: *originals can be up to 12 pages long (5,100 words), excluding bibliographical references and captions to figures and tables. It is not advisable to insert more than 10 images, including tables and figures. Colour illustrations and videos will not represent an economic charge for the authors, but the insertion of videos, for technical reasons, will be previously agreed with the editor. However, the editing method of RAPD Online allows, in specific cases, the acceptance of longer manuscripts, or the inclusion of a greater number of images, provided that the characteristics of the material presented so require. It is not advisable to have more than 9 authors, except in the case of collaborative works. In these originals, the first nine participants will be listed at the head of the paper and the rest of the participants will be listed at the end of the first page of the manuscript.*

Through the Manuscript Centre, the following information will be required for the submission of an original:

- General data:

1° Full title of the paper in Spanish and English
2° Surnames and first names of all authors.
3° Centre(s) of origin(s) (department, institution, city and country).
4° Full postal address of the responsible author, to whom correspondence should be addressed, including telephone, fax and email address.
5° Declaration on the existence or non-existence of a source of funding for the work, or conflicts of interest.

- Main body of the manuscript, containing:

1° Structured abstract in Spanish (optional also in English) and 3-5 keywords. The abstract will have a maximum length of 250 words and should be structured as follows:

a) Introduction and objectives
b) Material and methods
c) Results
d) Conclusions

2° List of abbreviations used in the text.

3° Text: it will include the following sections:
a) Introduction
b) Material and methods
c) Results

d) Discussion
e) Conclusions; each of them appropriately headed.

4° Bibliography: according to the specifications established in the group of common standards (See common standards and other supporting documents).

5° Acknowledgements.

6° Figure captions.

7° Tables and figures in text.

Thematic Reviews: *texts on Thematic Reviews can be up to 15 pages long (6,375 words), excluding bibliographical references and captions to figures and tables, and chapters corresponding to Update series up to 20 pages (8,500 words). In both cases the number of inserted images should not exceed 15, including tables and figures. However, the RAPD Online editing method allows, in specific cases, for manuscripts of greater length, or the inclusion of a greater number of images, provided that the characteristics of the material presented so require. Illustrations in colour will not be charged to the authors. Exceptionally, the inclusion of videos will be accepted. It is not advisable to include more than 4 authors per chapter.*

Through the Manuscript Centre, and for the submission of Reviews and Issues and Updates, the following information will be required:

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1° Full title of the work (in Spanish and English).
2° Surnames and first names of all authors.
3° Centre(s) of origin(s) (department, institution, city and country).
4° Full postal address of the responsible author, to whom correspondence should be addressed, including telephone, fax and email address.
5° Declaration on the existence or non-existence of a source of funding for the work, or conflicts of interest.

- Main body of the manuscript, containing:

1° Structured abstract in Spanish and English. 3-5 key words. The abstract will have a maximum length of 350 words, emphasising the most important aspects of the manuscript.
2° Text: Structured according to the criteria of the author(s), for a better understanding of the topic developed.
3° Bibliography: According to the specifications established in the group of common standards (See common standards and other supporting documents).
4° Acknowledgements.
5° Figure captions
6° Tables and Figures in the text.

Consensus documents: texts on Consensus documents are not limited in length in terms of text or images and tables. Exceptionally, the inclusion of videos is allowed. It is not advisable to have more than 10 authors per chapter.

Through the Manuscript Centre, and for the submission of Reviews and Updates, the following information will be required:

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1° Full title of the work in Spanish and English).
2° Surnames and first names of all authors.
3° Centre(s) of origin (department, institution, city and country).
4° Full postal address of the responsible author, to whom correspondence should be addressed, including telephone, fax and email address.
5° Declaration on the existence or non-existence of a source of funding for the work, or conflicts of interest.

- Main body of the manuscript, containing:

1° Structured abstract in Spanish and English. 3-5 key words. The abstract will have a maximum length of 350 words, emphasising the most important aspects of the manuscript.
2° Text: Structured according to the criteria of the author(s), for a better understanding of the topic developed.
3° Bibliography: According to the specifications established in the group of common standards (See common standards and other supporting documents).
4°Acknowledgements
5° Figure captions.
6° Tables and Figures in the text.

Clinical Cases: *the manuscripts included in this section will include 1-5 clinical cases, which due to their infrequent or unusual clinical behaviour, or because they provide some diagnostic or therapeutic novelty, deserve to be reported.*

The length of the texts in the Clinical Cases section should not exceed 5 pages (2,125 words), excluding bibliographical references and captions to figures and tables, and the number of inserted images should not exceed 5, including tables and figures. However, the RAPD Online editing method allows, in specific cases, the acceptance of longer manuscripts, or the inclusion of a greater number of images, provided that the characteristics of the material presented so require. Colour illustrations and videos will not represent a financial charge for authors, but the insertion of videos, for technical reasons, will be previously agreed with the editor. No more than 5 authors will be admitted, except in specific and reasoned cases.

Through the Manuscript Centre, and for the submission of Clinical Cases, the following information will be required:

- General data:

1° Full title of the paper in Spanish (optional also in English).
2° Surnames and first names of all authors.
3° Centre(s) of origin(s) (department, institution, city and country).
4° Full postal address of the responsible author, to whom correspondence should be addressed, including telephone, fax and e-mail address.

- Main body of the manuscript, containing:

1° Structured abstract in Spanish and English. 3-5 key words. The abstract will have a maximum length of 250 words.
2° Introduction. To present the clinical problem reported.
3° Description of the clinical case.
4° Discussion. To highlight the peculiarities of the case and its consequences.
5° Bibliography: According to the specifications established in the group of common standards (See common standards and other supporting documents).
6°Acknowledgements.7° Figure captions.
8° Tables and text figures.

Clinical Cases with Videos or Videoforum: *the manuscripts included in this section will include 1-5 clinical cases, which due to their infrequent or unusual clinical behaviour, or because they provide some diagnostic or therapeutic novelty, deserve to be communicated.*
The length of the texts in the Videoforum section should not exceed 5 pages (2,125 words), excluding bibliographical references and captions to figures and tables, and the number of images inserted should not exceed 5, including tables and figures. However, the RAPD Online editing method allows, in specific cases, the acceptance of longer manuscripts, or the inclusion of a greater number of images, provided that the characteristics of the material presented so require. Colour illustrations and videos will not represent a financial charge for authors, but the insertion of videos, for technical reasons, will be previously agreed with the editor. No more than 5 authors will be admitted, except in specific and reasoned cases.

Videos should be submitted in AVI, MPEG, MP4 OR MOV format, and at a recommended high quality resolution (720p or 1080p). They must not contain personal data of the patients. It is recommended that they be edited to minimise editing time, which should not exceed 10 minutes. If the video includes sound, it must be processed in MP3 format. If the videos to be included are in other formats, please contact the publisher

to verify their validity. They should not exceed 2GB.
Through the Manuscript Centre, and for the submission of Clinical Cases - Videoforum, the following information will be required:

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1° Full title of the work in Spanish and English. 2° Surnames and first names of all authors.
3° Centre(s) of origin (department, institution, city and country).
4° Full postal address of the responsible author, to whom correspondence should be addressed, including telephone, fax and email address.

- Main body of the manuscript, containing:

1° Structured abstract in Spanish and English. 3-5 key words. The abstract will have a maximum length of 250 words.
2° Introduction. To present the clinical problem reported. 3° Description of the clinical case.
4° Discussion. To highlight the peculiarities of the case and its consequences.
5° Bibliography: According to the specifications established in the group of common standards (See common standards and other supporting documents).
6°Acknowledgements.7° Figure captions.
8° Tables and figures in text.
9° Videos.

Link tutorial videos: https://www.sapd.es/videoteca/varios/ tutoriales/

Images of the month: *the manuscripts included in this section can take two formats, depending on the authors' preference.*

- Format A. Images with educational value: these shall include images of any kind, clinical, radiological, endoscopic, anatomopathological, macro and microscopic, which contribute to postgraduate training and therefore deserve to be shown because of their peculiarity, or because they represent a characteristic example.
- Format B. Key images for a diagnosis: These will include images of any kind, clinical, radiological, endoscopic, anatomopathological, macro and microscopic, together with a summarised clinical history, which will provide the possible final diagnostic resolution. This will be presented in a separate section in the same issue of the journal.

The length of the texts in the Images of the Month section must not exceed 1 page (425 words) in the clinical approach to the image presented and 2 pages (850 words), excluding bibliographical references and captions to figures and tables, in the commentary on the image (Format A) or in the diagnostic resolution of the case (Format B). However, the RAPD Online editing method allows, in specific cases, the acceptance of longer manuscripts, or the inclusion of a greater number of images, provided that the characteristics of the material presented so require. Colour illustrations and videos will not represent a financial charge for authors, but the insertion of videos, for technical reasons, will be previously agreed with the editor. No more than 3 authors will be accepted, except in specific and reasoned cases.

Through the Manuscript Centre, and for the submission of an Image of the Month, the following information will be required:

-General data:

1° Full title of the work in Spanish and English.. 2° Surnames and first names of all authors.
3° Centre(s) of origin (department, institution, city and country).
4° Full postal address of the responsible author, to whom correspondence should be addressed, including telephone, fax and email address.
5° Type of Image of the Month format chosen.

-Main body of the manuscript, containing:

1° Structured abstract in Spanish and English and 3-5 key words. The abstract will have a maximum length of 250 words.
2° Description of the image.
3° Comments on the image.
4° Bibliography: According to the specifications established in the group of common standards (See common standards and other supporting documents).
5° Figure captions.

New developments and updates in gastroenterology and hepatology: this section will be devoted to commenting on the scientific and medical developments that have occurred in recent years in the speciality of Gastroenterology and Hepatology.

This section will systematically and periodically analyse all facets of the speciality.

Texts on " New developments in Gastroenterology" may be up to 5 pages long (2,125 words), excluding bibliographical references and captions to added figures and tables. In both cases the number of inserted images must not exceed 5, including tables and figures. However, the RAPD Online editing method allows,

in specific cases, the acceptance of longer manuscripts, or the inclusion of a greater number of images, provided that the characteristics of the material presented so require. It is not advisable to have more than 3 authors per chapter.

Through the Manuscript Centre, you will be asked to provide the following information:

- General data:

1° Name of the bibliographic area reviewed and period analysed 2° Surname and first name of all authors. It is advisable to place a hyphen between the first and second surname.
3° Centre(s) of origin (department, institution, city and country).
4° Full postal address of the responsible author, to whom correspondence should be addressed, including telephone, fax and email address.
5° Declaration on the existence or non-existence of a source of funding for the work, or conflicts of interest.

- Main body of the manuscript, containing:

1° Structured abstract in Spanish and English. 3-5 key words. The abstract will have a maximum length of 250 words.
2° Description of the bibliographic material analysed.
3° Critical comments on the results contained in the selected works.
4° Bibliography: According to the specifications established in the group of common standards (See common standards and other supporting documents). If two or more originals have been chosen for the analysis, it is advisable to divide the section into sections at the authors' discretion.
5° Figure captions.
6° Tables and Figures in text.

Letters to the Editor: *this section will be dedicated to comments on any manuscript published in RAPD Online. This section may also include comments of a more general nature, establishing the authors' own hypotheses and suggestions, within the scientific field of Gastroenterology. The length of the texts in this section of Letters to the Editor should not exceed 2 pages (850 words), including bibliographical references. Two figures or tables may be included and the number of authors should not exceed four.*

Through the Manuscript Centre, and for the submission of a Letter to the Editor, the following information will be required:

- General data:

1° Full title of the work in Spanish and English.
2° Surnames and first names of all authors. It is advisable to place a hyphen between the first and second surname.
3° Centre(s) of origin (department, institution, city and country).
4° Full postal address of the responsible author, to whom correspondence should be addressed, including telephone, fax and e-mail address.
5° Declaration on the existence or non-existence of a source of funding for the work, or conflicts of interest.

- Basic body of the manuscript, containing:

1° Text of the manuscript.
2° Bibliography: According to the specifications set out in the common standards group (See common standards and other supporting documents).

B)Common standards and other supporting documents

This refers to the set of mandatory standards, both for uniformity in the presentation of manuscripts and for compliance with current legal regulations. In general, the style of manuscripts should follow the guidelines set out in the Vancouver Agreement of the International Committee of Medical Journal Editors. (http://www.ICMJE.org).

Units, generic names and abbreviations:

- Units. Biochemical and haematological parameters shall be expressed in International Units (SI), except haemoglobin which shall be expressed in g/dL. Length, height and weight measurements shall be expressed in decimal metric units and temperatures in degrees Celsius. Blood pressure shall be measured in millimetres of mercury.
There is an aid for the conversion of non-international (non-SI) units into international (SI) units. (http://www.techexpo.com/techdata/techcntr.html).

- Generic names. The generic names of medicinal products, clinical instruments and tools and software shall be used. When a brand name is the subject of research, the brand name and the name of the manufacturer, city and country shall be included in parentheses the first time the generic name is mentioned in the Methods section.

- Abbreviations. Abbreviations should be avoided, but if they have to be used, in order not to repeat long technical names, the full word should appear the first time in the text, followed by the abbreviation in brackets, which will already be used in the manuscript.

Bibliographical references: bibliographical references should be presented in the order in which they appear in the manuscript, with a sequential number, which will appear in the appropriate place in the text, in brackets. This numbering will be maintained and will serve to order the list of all references at the end of the manuscript, as normal text and never as a footnote. Personal communications and unpublished data will not be included in the final list of bibliographical references, although they will be mentioned in the appropriate place in the text, in brackets, as appropriate, i.e. personal communication or unpublished data. When the bibliographic citation includes more than 6 authors, the first 6 authors should be cited, followed by the abbreviation et al.

The style of bibliographic references will depend on the type and format of the source cited:

- Medical journal article: journal names should be abbreviated according to the style of the Index. Medicus/Medline (http://www.ncbi.nlm.nih.gov/journals?itool=sidebar).

- Article already published in print and online journals Internet:
The authors (surname and initial of the first name, comma separation between authors), the full name of the manuscript, the abbreviation of the journal, the year of publication and after a semicolon the volume of the journal and after a colon the complete numbers of the first and last page of the paper.

Kandulsky A, Selgras M, Malfertheiner P. Helicobacter pylori infection: A Clinical Overview. Dig Liver Dis 2008; 40:619-626.

Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK,Cancado EL, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 1999; 31:929-938.

- Admitted article, published only on the Internet, but not yet included in a regular number of the journal: the authors, the full name of the manuscript, the abbreviation of the journal, the year and month since the article is available on the Internet and DOI will be noted. The original paper to which reference is made usually details how to cite the manuscript.

Stamatakos M, Sargedi C, Stefanaki C, Safi oleas C, Matthaiopoulou I, Safi oleas M. Anthelminthic treatment: An adjuvant therapeuticstrategy against Echinococcus granulosus. Parasitol Int (2009), doi:10.1016/j.parint.2009.01.002

Inadomi JM, Somsouk M, Madanick RD, Thomas JP, Shaheen NJ. A cost-utility analysis of ablative therapy for Barrett'sesophagus, Gastroenterology (2009), doi: 10.1053/j.gastro.2009.02.062.

- Article from a journal that is published only on the Internet, but arranged in a conventional way: the authors, the full name of the manuscript, the abbreviation of the journal (can be added in brackets online), the year of publication and after a semicolon the volume of the journal and after a colon the complete numbers of the first and last page of the paper. If the original work being referenced provides the DOI and Internet address (URL), these can be added at the end of the reference.

Gurbulak B, Kabul E, Dural C, Citlak G, Yanar H,Gulluoglu M, et al. Heterotopic pancreas as a leading point for small-bowel intussusception in a pregnant woman. JOP (Online) 2007; 8:584-587.

Fishman DS, Tarnasky PR, Patel SN, Raijman I. Managementof pancreaticobiliary disease using a new intra-ductal endoscope: The Texas experience. World J Gastroenterol 2009; 15:1353-1358. Available from: URL: http://www.wjgnet.com/1007-9327/15/1353.asp. DOI: http://dx.doi.org/10.3748/wjg.15.1353

- Article from a journal that is published only on the Internet, but is not conventionally arranged: the authors, the full name of the manuscript, the abbreviation of the journal, the year of publication and the DOI will be listed.

Rossi CP, Hanauer SB, Tomasevic R, Hunter JO, Shafran I, Graffner H. Interferon beta-1a for the maintenance of remission in patients with Crohn's disease: results of a phase II dose-finding study.BMC Gastroenterology 2009, 9:22doi:10.1186/1471-230X-9-22.

-Article published in an abstract or in a supplement of a journal: the authors (surname and first initial, separated by commas between authors), the full name of the manuscript, the word abstract in square brackets, the abbreviation of the journal, the year of publication and after a semicolon the volume of the journal, followed by the abbreviation Suppl, or Supl, in brackets and after a colon the complete numbers of the first and last page of the paper.

Klin M, Kaplowitz N. Differential susceptibility of hepatocytesto TNF-induced apoptosis vs necrosis [Abstract]. Hepatology 1998; 28(Suppl):310A.

- Books: the authors of the book (surname and first initial, comma separated by the authors), the title of the book, the city where it was published, the name of the publisher and the year of publication will be listed.

Takada T. Medical Guideline of Acute Cholangitis and Cholecystitis. Tokyo: Igaku Tosho Shuppan Co; 2005.

- Chapter of a book: the authors of the chapter should be listed (surname and first initial, separated by commas between authors), followed by In: the names of the editors of the book and, after a full stop, the name of the book. The city where it was published, the name of the publisher, the year of publication and after a colon the complete numbers of the first and last page of the work.

Siewert JR. Introduction. In: Giuli R, Siewert JR, Couturier D, Scarpignato C, eds. OESO Barrett's Esophagus. 250 Questions. Paris: Hors Collection, 2003; 1–3.

- Information from a document produced at a meeting: this type of reference should be avoided whenever possible. However, if it has to be cited, the title of the subject, the name of the meeting and the city where it was held should be given. The entity that organised the meeting, and the year. The e-mail address through which the document can be accessed.

U.S. positions on selected issues at the third negotiating session of the Framework Convention on Tobacco Control. Washington, D.C.: Committee on Government Reform, 2002. (Accessed March 4, 2002, at:http://www.house.gov/reform/min/inves_tobacco/index_accord. htm.)

Figures, tables and videos: iconography, whether photographs, radiographs, diagrams or graphs, should be referred to under the generic name of "Figure". References to figures, tables and videos should be highlighted in bold. They should be numbered with Arabic numerals, according to their order of appearance in the text. Panels of two or more photographs grouped together will be considered as a single figure and may be referred to as "Figures 1A, 1B, 1C".

- Photographs: photographs should be sent in digital format TIFF (.TIF), JPEG (.JPG) or BMP, in black and white or colour, well contrasted, with an appropriate resolution (preferably 150-300 dots per inch). In the case of JPEG files, the minimum compression should be used to maintain maximum quality, i.e. in a non-reduced size.

X-ray, ultrasound, CT and MRI images, if not directly available in electronic format, should be scanned in grayscale and saved in JPG format.

Endoscopic images and other techniques generating colour images, if not directly available in electronic format, shall be scanned in colour. Special details shall be indicated by arrows, using for these and any other type of symbols the maximum contrast plot with respect to the figure.

Figure files will be identified according to their order of appearance in the text, with the name of the file, its number and surname of the first signatory (e.g.: fig1_Gómez.jpg) or the title of the article. Each image must have an associated figure caption that serves as a description. Figure captions must be submitted in a separate text document with clear reference to the figures to which they refer. Images may be inserted in Word/PowerPoint files to facilitate their identification or association with the figure captions, but they must always be submitted as separate images in the formats mentioned above.

Photographs of patients must not make them unidentifiable. If it is not possible to obtain them, the publication of the photograph must be accompanied by written permission (Model Photograph Permission Form).

- Diagrams, drawings, graphs and tables: diagrams, drawings, graphs and tables must be sent in digital format, as high resolution images or, preferably, in Word/PowerPoint format with editable text. Schemes, drawings, graphs or figures scanned from other publications will not be accepted. For diagrams, drawings, graphs, tables or any other figures, the colour black should be used for lines and text, and a light background, preferably white. If it is necessary to use several colours, easily distinguishable colours with high contrast to the background should be used. Graphics, symbols and letters should be of sufficient size to be clearly identifiable when reduced. Tables should be made with the -Table- tool (not with the use of tabulators and drawing lines or text boxes).

- Videos: videos must be submitted in AVI or MPEG format, processed with the CINEPAC RADIUS or MPEG codec and at a resolution of 720x576 or 320x288. It is recommended that they are edited to minimise their length, which should not exceed 2 minutes. If the video includes sound, it must be processed in MP3 format. If the videos to be included are in other formats, please contact the publisher to verify their validity. For the inclusion of videos in articles, prior authorisation must be obtained from the editorial board.

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Conflict of interest: *a conflict of interest exists when an author (or the author's institution), reviewer, or editor has, or has had in the last 3 years, financial or personal relationships with other persons, institutions, or organisations, which may unduly influence their activity.*
Authors must declare the existence or non-existence of conflicts of interest to the Manuscript Centre during the article submission process, but are not required to submit a Conflict of Interest Declaration Form when the manuscript is submitted. This will be required later, if necessary, when the manuscript is accepted.

Grants and financial support received by the authors for the research should be specified at the end of the manuscript in the Acknowledgements section.

Statistics: *it is not the aim of RAPD Online to provide an exhaustive description of the statistical methods used in the conduct of a research study, but to specify some requirements that should appear in manuscripts as standards of good practice. Authors can consult a basic document on this subject at: Bailar JC III, Mosteller F. Guidelines for statistical reporting in articles for medical journals: amplifications and explanations. (http://www.sapd.es/ public/guidelines_statistical_ articles_medical_ journals. pdf). Ann Intern Med 1988; 108:266-73.*

- The statistical methods used, as well as the computer programs and the name of the software used should be clearly stated in the Material and Methods Section.
- To express the mean, standard deviation and standard error, the following formats should be used: "mean (SD)" and "mean ± SE". To express the median, the interquartile range (IQR) values should be used.
- P should be used in capital letters, reflecting the exact value and not expressions such as less than 0.05, or less than 0.0001.
- Whenever possible, findings (means, proportions, odds ratios and others) should be quantified and presented with appropriate indicators of error, such as confidence intervals.
- Studies that show levels of statistical significance should include sample size calculations. Authors should report research losses, such as withdrawals from clinical trials.

Other documents and ethical standards

- Human research: publications on human research must state in a prominent place in the original that: a) written informed consent has been obtained from each patient, b) the study protocol conforms to the ethical standards of the Helsinki declaration of 1975 (https://www.wma.net/es/policies-post/declaracion-de- helsinki-de-la-amm-principios-eticos-para-las-investigaciones-medicas-en-seres-humanos/) and has been approved by the ethics committee of the institution where the study was conducted.

- Animal research: studies involving experimental animals must state in a prominent place in the original that they are cared for according to the criteria outlined in the "Guide for the Care and Use of Laboratory Animals" written by the National Academy of Sciences and published by the National Institutes of Health. (http://www.nap. edu/readingroom/books/labrats).

- Controlled clinical trials: The design of controlled clinical trials should follow the CONSORT guidelines, available at: http://www.consort-statement.org and be registered before starting the inclusion of patients.

- Microarray-derived data: must be submitted to a repository such as Gene Expression Omnibus or ArrayExpress prior to manuscript submission.

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ORIGINAL

PREGNANCY AND INFLAMMATORY BOWEL DISEASE: IMPACT OF GESTATION IN A TERTIARY CARE CENTER.

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Abstract

Introduction and objectives: Pregnancy is a relevant milestone in the clinical course of a patient with Inflammatory Bowel Disease (IBD). The objective was to evaluate the impact of adherence to the therapeutic plan in the course of pregnancy and to analyze variables related to disease activity, treatments received and pregnancy outcome.

Material and methods: single-center retrospective observational study in pregnant patients with IBD. Demographic variables related to the disease, treatment received and pregnancy outcomes were collected. Adherent group was defined as the group that agreed to the therapeutic plan. A non-adherent group was defined as those patients who did not agree to the therapeutic plan or who abandoned it during pregnancy.

Results: 32 patients were included, 56.3% diagnosed with Crohn's disease (CD) and 43.7% with Ulcerative Colitis (UC). Of those diagnosed with CD, 13 were in remission and 5 had moderate activity, compared to 11 in remission and 3 with mild activity in UC. Eleven (34.4%) patients abandoned treatment without consensus, and 12 (37.5%) patients had flares during pregnancy. Significant differences were found with respect to the number of flares and fetal birth weight. Differences were also found when comparing inflammatory activity at the beginning of pregnancy and the evolution of pregnancy.

Conclusion: The study data reinforce the importance of preconception counseling, activity control and adherence to the therapeutic plan, motivating us to improve the care and follow-up of our patients of gestational age.

Keywords: pregnancy, inflammatory bowel disease, preconception counseling.

Abbreviations

GETECCU: Spanish Working Group on Crohn's Disease and Ulcerative Colitis (original in Spanish Grupo Español de Trabajo de la Enfermedad de Crohn y la Colitis Ulcerosa) , Anti-TNF: tumor necrosis factor-alpha inhibitors, UC: ulcerative

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colitis, CD: Crohn's disease, IBD: inflammatory bowel disease, HBI: Harvey-Bradshaw activity index for Crohn's disease, TWI: modified Truelove-Witts activity index for Ulcerative Colitis, ECCO: European Crohn's and Colitis Organization.

Introduction

Inflammatory Bowel Disease (IBD) is the generic name for a group of diseases characterized by chronic, intermittent and uncontrolled inflammation of the intestinal mucosa[1]. The term "IBD" includes two main entities, Crohn's disease (CD) and ulcerative colitis (UC), both of which constitute a major health problem, with a prevalence of more than 0.5% of the population in industrialized countries[2] and an increasing incidence in newly industrialized countries[3].

The specific etiology of IBD is unknown; however, we know that both pathogenesis and clinical course are influenced by many factors, broadly characterized as genetic susceptibility factors, intestinal microflora, lifestyle, environmental factors and the immune system of patients. Specifically, it is currently believed that the disease develops in genetically susceptible subjects, due to a dysregulation of homeostasis between the commensal microflora and/or other environmental elements with the capacity to modify the patient's immune response, which presents an imbalance towards the perpetuation of the inflammatory process[4].

IBD usually affects young people with a peak incidence between 25 and 35 years of age. It can manifest with different clinical symptoms, including by analytical findings or incidentally with an imaging test. Although CD and UC share common features, they are distinguished by different pathophysiological aspects and clinical manifestations. CD is characterized by transmural and discontinuous inflammation that can affect any location of the gastrointestinal tract, mainly the terminal ileum and perianal region. On the other hand, in UC the inflammatory lesions are typically limited to the mucosa and affect the colon, starting in the rectum and with the possibility of extending to the rest of the large intestine. In addition, these diseases can affect other organs at a distance, giving rise to extraintestinal cutaneous, articular, ophthalmologic, hepatic manifestations, etc[5].

In women, this occurs during the years of greatest reproductive capacity. The implications of the disease and the medications used to treat it are important considerations for the gastroenterologist, maternal fetal medicine specialist and general obstetrician/gynecologist who evaluate and manage patients before, during and after pregnancy. Like other autoimmune conditions such as systemic lupus erythematosus or multiple sclerosis, women with IBD have higher rates of childlessness by choice and have lower birth rates than the general population[6], this trend being the result of misinformation regarding fertility, the safety of medications for themselves and the fetus, and the feasibility of inheriting the disease[7].

Women with IBD as a group have the same fertility rates as women in the age-matched control group; however, specific subgroups will have impaired fertility[8]. Active disease increases the rate of infertility as a result of inflammation affecting the fallopian tubes or ovaries, dyspareunia secondary to perianal disease, decreased libido, or depression[9] In women with inactive disease, infertility triples after pelvic surgery, related to post-surgical adhesions involving mainly the fallopian tubes[10], whereas procedures involving only the abdominal cavity and not invading the pelvis, including ileorectal anastomosis, do not seem to impair fertility[11].

On the other hand, patients with IBD appear to have a higher risk of pregnancy complications than the general population. Several studies have analyzed the impact of IBD on labor and delivery outcomes. According to their results, preterm deliveries, small-for-gestational-age newborns, low birth weight and spontaneous abortions (stillbirths) are more frequent in patients with IBD than in the general population[12]. Studies relating disease activity during pregnancy to birth outcomes show that active disease and disease severity are associated with worse birth outcomes in IBD patients[13]. In contrast, the use of IBD-related drugs during pregnancy does not seem to carry an excessive risk of complications in general, except for methotrexate, tofacitinib, upadacitinib, filgotinib and ozanimod, and if we look at the risk of infection during the first months of life, recent work has shown that the combination of anti-TNF and thiopurines does increase the risk of complications[14-18].

Fewer data are available on the long-term findings of children born to women with IBD. A study published in 2016 investigating whether children of women with IBD during pregnancy were at increased risk of long-term pediatric morbidity did not reveal any detrimental effect of maternal IBD on child health[19].

All this evidence supports that pregnancy is an extremely important event in the life of patients with IBD, representing a major impact on the clinical course of the disease. The importance of disease activity, and thus of the treatment these patients receive, may determine the course of pregnancy and

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the health of the fetus. Given the increasing evidence year after year of the safety of the use of drugs during pregnancy and the reduced presence of fetal flares and complications, we decided to carry out this study.

Based on this hypothesis, our primary objective was to evaluate the impact of adherence, or lack thereof, to the therapeutic plan for disease control during pregnancy proposed by the referring physician. The participating patients were those included in the registry of the Virgen de la Victoria University Hospital and who gave birth up to March 2023. Secondary objectives were to evaluate the relationship between treatment discontinuation and the appearance of disease activity, as well as to analyse the development of gestation (duration) in these patients, the type of delivery and foetal birth weight.

Material and methods

Study population and design

We conducted a single-centre retrospective observational study of patients over 18 years of age diagnosed with IBD [Crohn's disease (CD) or ulcerative colitis (UC)] by clinical, radiological, endoscopic or histological criteria who were being followed up at the Virgen de la Victoria Hospital in Malaga and who were included between January 2021 and March 2023 in our own register of pregnant patients, after signing an informed consent form in a monographic consultation on IBD during pregnancy.

Of all the patients included in the registry, participants who lost follow-up during pregnancy and those who had not completed gestation before March 1, 2023 were excluded.

This project was implemented following the guidelines of the Declaration of Helsinki (Fortress 2013) and the Good Clinical Practice Guidelines. Personal data were processed according to REGULATION (EU) 2016/679 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27 April 2016 on the protection of individuals with regard to the processing of personal data and on the free movement of such data. Patients were not identified by name in the document and only the study investigators had access to their data.

Informed consents were not required from the patients, since only the review of the digital medical records was carried out.

Variables studied

The following variables were collected: age, smoking, IBD-related variables (type of IBD, Montreal Classification [Annex 1], disease activity at the beginning of pregnancy [Annex 2], previous intestinal surgery, years from diagnosis of the disease to conception), characteristics related to treatment before and during pregnancy (type of treatment before the beginning of pregnancy, presence of flares during pregnancy, treatment during flares, number of treatment discontinuations and trimester of discontinuation. A worsening of symptoms with respect to their baseline situation was accepted as a flare-up and, after ruling out other possible causes, was attributed to their IBD) and variables related to pregnancy and conception (previous abortions, evolution of the pregnancy and weeks of gestation of the pregnancy, end of delivery by cesarean section and weight of the newborn).

Treatment adherence groups

The adherent group was defined as the one whose patients agreed on the therapeutic plan with their referring physician, including both patients who did not discontinue treatment during the entire pregnancy and those who discontinued treatment on a scheduled basis in the third trimester.

On the other hand, non-adherent patients group was defined as the one in which the patients either did not reach a consensus on the therapeutic plan, refusing to initiate or modify any treatment, or abandoned the medical advice during pregnancy, voluntarily discontinuing treatment before the third trimester.

Statistical study

Quantitative variables were shown as mean and range. Qualitative variables were shown as numerical value and percentage. Quantitative variables were compared with the t-test and qualitative variables were contrasted with the chi-square test. A statistically significant result was considered when the p value was <0.05.

Statistical analysis was carried out with the support of IBM-SPSS statistics version 29 (SPSS INc., Chicago, USA).

Results

Of the 39 patients initially assessed for inclusion, 7 were excluded (4 for not having given birth by March 2023 and 3

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for loss to follow-up), leaving 32 patients in the final analysis (Figure 1).

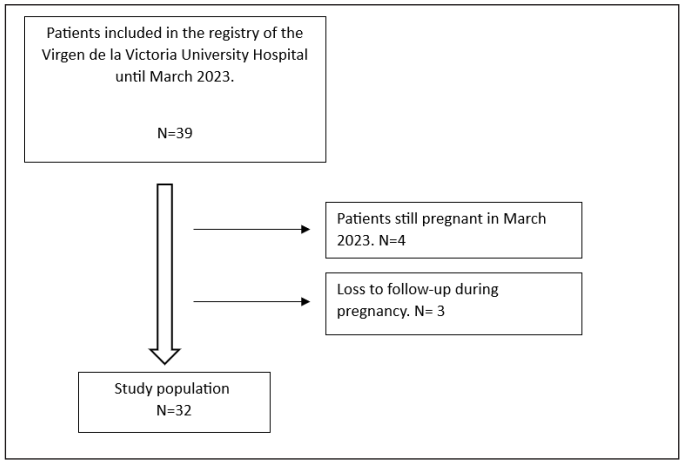

Figure 1. ***Flow diagram of the study population.***

Demographic variables and smoking

The mean age was 31.1 years (23-40), with a total of 5 patients (15.6%) smoking (Table 1).

Variables related to the underlying disease

Variables on baseline disease characteristics are shown in Table 1.

Eighteen patients were diagnosed with CD (56.3%) and 14 with UC (43.7%). The mean time from diagnosis to conception of 8.1 years (1-22).

Patients with CD were grouped according to the Montreal Classification, as follows: According to age (A): 2 (11.1%) corresponded to A1, 16 (88.9%) corresponded to A2 and none to A3. According to location (L): 9 (50%) were L1, 1 (5.5%) were L2 and 8 (44.5) were L3. According to behavior (B): 12 (66.7%) had phenotype B1, 1 (5.5) B2 and 5 (27.8%) corresponded to B3.

Patients with UC had the following characteristics according to the Montreal Classification. According to extension (E): 5 (35.7%) patients were E1, 5 (35.7%) corresponded to E2 and 4 (28.6%) E3. According to the severity at diagnosis recorded in the history (S): 6 (42.8%) were S0, 6 (42.8%) corresponded to S1 and 2 (14.4%) to S2.

Regarding disease activity at the beginning of pregnancy, the Harvey-Bradshaw index was used for patients with CD, with the following results: 13 (72.2%) were in remission and 5 (27.8%) had moderate activity. For UC patients, the modified Truelove-Witts index was used, with the following findings: 11 (78.6%) were in remission and 3 (21.4%) had mild activity.

Of the total patients, 2 (6.2%) had or had had perianal disease (2 CD), while 7 (21.9%) patients had required IBD-related surgery at some point.

Variables related to treatment for IBD

The variables on the characteristics of IBD treatment are shown in Table 2.

Regarding the treatment received by the patients prior to pregnancy, it was distributed as follows: 2 (6.2%) were not receiving treatment, 12 (37.5%) were taking aminosalicylates, 5 (15.6%) were receiving thiopurines, 1 (3.1%) was taking the combination corticosteroids + thiopurines, 2 (6.2%) the combination aminosalicylates + thiopurines, 3 (9.4%) the triple therapy aminosalicylates, thiopurines and AntiTNF, 1 (3.1%) thiopurines + AntiTNF, 1 (3.1%) isolated AntiTNF and 5 (15.6%) were on Ustekinumab therapy.

Regarding treatment discontinuation, a total of 15 (46.9%) patients discontinued treatment, of whom 4 (12.5%) did so by consensus with their referring physician in the third trimester. On the other hand, 11 (34.4%) patients abandoned treatment without consensus with their physician, of which 9 (28.1%) were in the first trimester and 2 (6.2%) in the second trimester.

Of all the patients included in the study, 12 (37.5%) suffered flare-ups during pregnancy.The treatment received to deal with the flares was distributed as follows: 3 (9.4%) patients refused treatment, 4 (12.5%) received locally acting corticosteroids, 1 (3.1%) required both locally acting and systemic corticosteroids, 1 (3.1)% aminosalicylates and 3 (9.4%) required both aminosalicylates and locally acting corticosteroids.

Pregnancy-related variables

The variables on pregnancy characteristics are shown in Table 3.

Of the 32 patients included, 13 (40.6%) had had at least one previous miscarriage. Regarding the evolution of the pregnancy, 26 (81.2%) carried the pregnancy to term, while 6 (18.8%) had a miscarriage. Of these, 1 (3.1%) was in the first trimester, 4 (12.5%) occurred in the second trimester and 1 (3.1%) took place in the third trimester.

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Variables		Total, N=32
Mean age, years (range)		31.1 (23-40)
Smoking, n (%)		5 (15.6%)
Type of IBD	UC	14 (43.7%)
	CD	18 (56.3%)
C. montreal, n (%) Crohn's disease (n=18)		
Age	A1	2 (11.1%)
	A2	16 (88.9%)
	A3	0(0%)
Location	L1	9 (50%)
	L2	1 (5.5%)
	L3	8 (44.5%)
	L4	0 (0%)
Behaviour	B1	12 (66.7%)
	B2	1 (5.5%)
	B3	5(27.8%)
Ulcerative colitis (n=14)		
Extent	E1	5 (35.7%)
	E2	5 (35.7%)
	E3	4 (28.6%)
Severity	S0	6 (42.8%)
	S1	6 (42.8%)
	S2	2 (14.4%)
	S3	0 (0%)
Disease activity in early pregnancy, n (%)		
Crohn's disease (n=18)		
	Remission (HBI 0-4)	13 (72.2%)
	Mild activity (HBI 5-7)	0 (0%)
	Moderate activity (HBI 8-16)	5 (27.8%)
	Severe activity (HBI >17)	0 (0%)
Ulcerative colitis (N=14)		
	Remission (TWI <11)	11 (78.6%)
	Mild activity (TWI 11-15)	3 (21.4%)
	Moderate activity (TWI 16-21)	0 (0%)
	Severe activity (TWI >21)	0 (0%)
Perianal disease, n (%)		2 (6.2%)
Intestinal surgery for IBD, n (%)		7 (21.9%)
Years from IBD diagnosis to conception, years (range)		8.1 (1-22)

IBD: inflammatory bowel disease, UC: ulcerative colitis, CD: crohn's disease, HBI: harvey-bradshaw index, TWI: truelove-witts modified index.

Table 1. ***Demographic characteristics.***

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Variables		Total, N=32
Treatment prior to start of pregnancy, n (%)		
	No treatment	2 (6.2%)
	Aminosalicylates	12 (37.5%)
	Corticosteroids	0 (0%)
	Thiopurines	5 (15.6%)
	Methotrexate	0 (0%)
	Thiopurines + Corticosteroids	1 (3.1%)
	Aminosalicylates + thiopurines	2 (6.2%)
	Aminosalicylates + thiopurines + AntiTNF	3 (9.4%)
	Thiopurines + AntiTNF	1 (3.1%)
	AntiTNF	1 (3.1%)
	Ustekinumab	5 (15.6%)
	Vedolizumab	0 (0%)
	Tofacitinib	0 (0%)
Treatment dropout, n (%)		16 (50 %)
With medical consensus= 4 (12,5%)		
	Before pregnancy	0 (0%)
	First trimester	0 (0%)
	Second trimester	0 (0%)
	Third trimester	4 (12.5 %)
Without medical consensus= 11 (34,4%)		
	Before pregnancy	0 (0%)
	First trimester	9 (28.1%)
	Second trimester	2 (6.2%)
	Third trimester	0 (0%)
Flares during pregnancy, n (%)		12(37.5%)
Treatment of flares in pregnancy, n (%)		
	No treatment	3 (9.4%)
	Locally acting corticosteroids	4 (12.5 %)
	Systemic corticosteroids	0 (0%)
	Locally acting + systemic corticosteroids	1 (3.1%)
	Aminosalicylates	1 (3.1%)
	Aminosalicylates + locally acting corticosteroids	3 (9.4%)

AntiTNF: Anti Tumour Necrosis Factor Alpha.

Table 2. ***Treatment-related characteristics before and during pregnancy.***

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Variables		Total, N=32
Previous miscarriages, n (%)		13 (40.6%)
Course of pregnancy, n (%)		
	Delivery	26 (81.2%)
	Abortion	6 (18.75)
Trimester of abortion, n (%)		
	First trimester	1 (3.1%)
	Second trimester	4 (12.5%)
	Third trimester	1 (3.1%)
Weeks of gestation at delivery, weeks (range)		37.3 (30-41)
Cesarean delivery, n (%)		14 (43.7%)
Fetal birth weight, grams (range)		2919 (2070-3820)

Table 3. ***Pregnancy characteristics.***

The mean duration from gestation to delivery was 37.3 weeks (30-41), with cesarean delivery occurring on 14 (43.7%) occasions.

The mean birth weight of the neonates was 2919 grams (2070-3820).

Inferential analysis

The results of the comparison of the demographic, treatment-related and pregnancy-related variables between the adherent and non-adherent groups to the therapeutic plan are shown in Table 4. Statistical significance (p<0.01) was found in the variable flares during pregnancy: 3 (14.3%) patients in the adherent group presented flares during pregnancy compared to 9 (81.8%) in the non-adherent group (Figure 2).

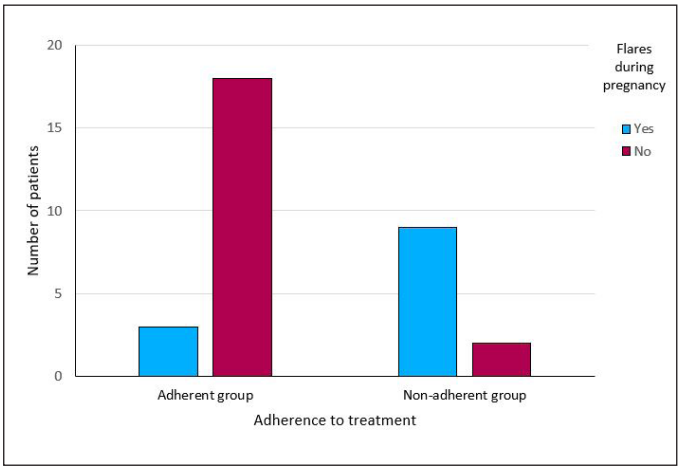

Figura 2. ***Flares during pregnancy.***

When comparing the variable fetal birth weight in both groups, a mean of 3073 grams (2080-3820) was obtained in the adherent group versus 2500 grams (2070-3090) in the non-adherent group, these differences reaching statistical significance (p = 0.025).

When comparing the variables inflammatory activity at the beginning of the pregnancy and evolution of the pregnancy, it was found that none (0%) of the patients in remission, 1 (3.1%) in the group with mild activity and 5 (15.6%) with moderate activity had miscarriage, these differences reaching statistical significance (p<0.01) (Figure 3).

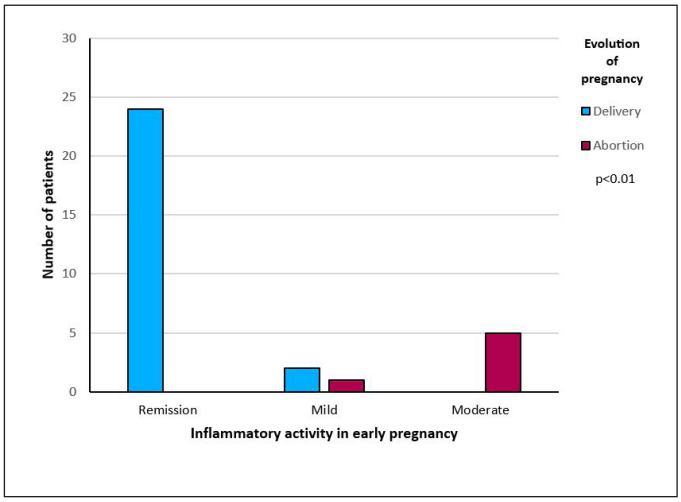

Figura 3. ***Inflammatory activity at the beginning of pregnancy and evolution of pregnancy.***

On the other hand, when comparing the type of treatment prior to pregnancy in relation to adherence or non-

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adherence to the therapeutic plan, statistical significance was not reached (p=0.631) (Figure 4).

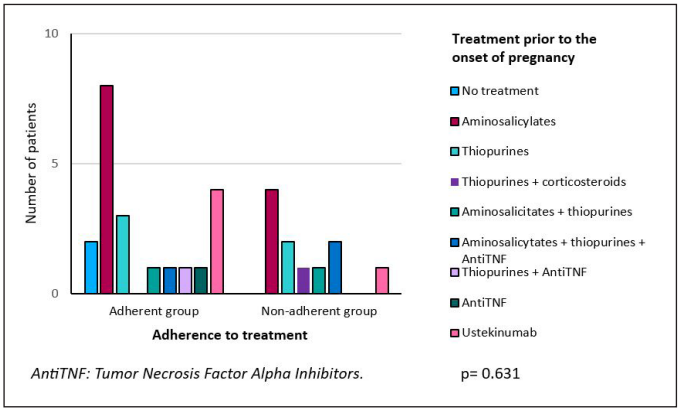

Figure 4. ***Type of previous treatment received.***

Discussion

In the study published by Aboubakr *et al*[20], where the opinions of 116 patients with IBD and genetic desire were collected, the safety of treatments for the disease and the effect of IBD on fertility and pregnancy were identified as the main concerns of the participants. Although there are no data indicating worse fertility and miscarriage rates in patients with CD compared to UC in similar situations, a systematic review by Walldorf *et al*[21] showed that patients with CD voluntarily stop having children more frequently than patients with UC, with less knowledge about the disease being the main limiting factor in most cases[22].

For this reason, preconception counseling for IBD patients of childbearing age is of utmost importance to ensure correct knowledge about the disease, treatment options and implications for pregnancy, as reflected in the work of Mountifield *et al*[23].

In our study, the importance of preconception counseling and adherence to the therapeutic plan is evidenced by the higher rate of flares during pregnancy in the nonadherent group compared to the adherent group (81.8% vs 14.3%), with these differences reaching statistical significance (p<0.01). These data are in line with those published in the meta-analysis by Abhyankar *et al*,[24] in which more than 1600 patients diagnosed with UC and CD were evaluated, showing that irregular therapeutic follow-up and the presence of active disease prior to conception increase the risk of flares during pregnancy. This last fact also showed differences in our study, without reaching statistical significance (p=0.151). We suspect that the power of the study was not sufficient to reach it.

The consequences of inflammatory bowel activity during pregnancy are discussed in the work of Ban *et al*.[25] where more than 9000 patients with IBD were included and compared with more than 2 million patients without IBD. The data show lower live birth rates (46.2/1000 person-years vs. 49.3/1000 person-years), lower adjusted fertility rates during flares (0.7 vs. 0.93) or after surgery (0.84 vs. 0.93). These data are reflected in our study, where the non-adherent group had a higher frequency of abortions than the adherent group (36.4% vs. 9.5%), with these differences being close to statistical significance (p=0.065). We did not find significant differences regarding the trimester of abortion between the two comparative groups (p= 0.269).

Furthermore, when comparing inflammatory activity with the evolution of pregnancy, we found that patients with mild and especially moderate activity had a higher incidence of miscarriage, while patients in remission were free of miscarriage, these differences being significant (p<0.01) (Figure 3).

Focusing on the type of delivery, the frequency of cesarean sections in our study showed differences between the adherent (38.1%) and non-adherent (54.5%) groups to the therapeutic plan, without reaching statistical significance (p=0.373), being more frequent overall in patients with IBD compared to the general population, as was evident in a Korean population study, where patients with IBD had a frequency of 46.5% compared to 38.8% in the general population[26] (OR: 1.43; 95% CI: 1. 17-1.75).

The differences between the groups under study are also shown by comparing the weeks of gestation at delivery and fetal birth weight. On the one hand, the adherent group presented a mean of 38 weeks of gestation at delivery (range 30-41) while the non-adherent group presented a mean of 35.4 (31-40), these differences being close to statistical significance (p=0.08) and in line with the data offered in the meta-analysis published by O'Toole *et al*.[27], where patients with IBD and activity during pregnancy more frequently presented preterm deliveries (OR: 1.85, 95%: 1.67-20.5). The cesarean section rate in our center between 2010 and 2020 was 27.7%, showing a marked increase in patients with IBD compared to the general population, being more marked in the non-adherent group.

In our study, the newborns of mothers belonging to the adherent group had a mean birth weight of 3073 grams (2080-3820) compared to 2500 grams (2070-3090) of newborns in the non-adherent group, with these differences reaching statistical significance (p<0, 05) and being concordant with that described in the meta-analysis published by Alyshah *et al*[28], where patients with IBD and active disease gave birth to

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Variables	Patients adhering to the therapeutic plan (n=21)	Patients not adherent to the therapeutic plan (n=11)	p
Mean age, years	31 (23-40)	31.6 (27-37)	0.978
Smoking, n (%)	2 (9.5%)	3 (27.3%)	0.189
Type of IBD, n of CD (%)	12 (57.4%)	6 (54.5%)	0.888
Disease activity at start of pregnancy, n (%)			0.151
Crohn's disease (n=18)	n=12	n=6	0.141
Remission (HBI 0-4)	10 (83.3%)	3 (50%)	
Mild (HBI 5-7)	0 (0)	0 (0)	
Moderate (HBI 8-16)	2 (16.7%)	3 (50%)	
Severe (HBI >17)	0 (0)	0 (0)	
Ulcerative colitis (n=14)	n=9	n=5	0.168
Remission (TWI <11)	8 (88.8%)	3 (60%)	
Mild (TWI 11-15)	1 (11,2%)	2 (40%)	
Moderate (TWI 16-21)	0 (0)	0 (0)	
Severe (TWI >21)	0 (0)	0 (0)	
Intestinal surgery for IBD, n (%)	5 (23.8%)	2 (18.2%)	0.715
Years from IBD diagnosis to conception, years (range)	9.5 (1-22)	5.4 (1-12)	0.052
Treatment prior to onset of pregnancy, n (%)			0.631
No treatment	2 (9.5%)	0 (0)	
Aminosalicylates	8 (38.1%)	4 (36.4%)	
Corticosteroids	0 (0)	0 (0)	
Methotrexate	0 (0)	0 (0)	
Thiopurines	3 (14.3%)	2 (18.2%)	
Thiopurines + Corticosteroids	0 (0)	1 (9.1%)	
Aminosalicylates + thiopurines	1 (4.8%)	1 (9.1%)	
Aminosalicylates + thiopurines + AntiTNF	1 (4.8%)	2 (18.2%)	
Thiopurines + AntiTNF	1 (4.8%)	0 (0)	
Anti-TNF	1 (4.8%)	0 (0)	
Ustekinumab	4 (19%)	1 (9.1%)	
Vedolizumab	0 (0)	0 (0)	
Tofacitinib	0 (0)	0 (0)	
Flares during pregnancy, n (%)	3 (14.3%)	9 (81.8%)	<0.01*
Treatment of flares in pregnancy, n (%)			0.299
No treatment	1 (4.8%)	2 (18.2%)	
Locally acting corticosteroids	0 (0)	4 (36.4%)	
Systemic corticosteroids	0 (0)	0 (0)	
Locally acting corticosteroids + systemic corticosteroids	1 (4.8%)	0 (0)	

Table 4. ***Inferential analysis of the variables with respect to the adherence group (Part 1).***

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Variables	Patients adhering to the therapeutic plan (n=21)	Patients not adherent to the therapeutic plan (n=11)	p
Aminosalicylates + locally acting corticosteroids	1 (4.8%)	2 (18.2%)	
Aminosalicylates	0 (0)	1 (9.1%)	
Previous abortions, n (%)	8 (38.1%)	5 (45.4%)	0.687
Pregnancy course, n (%)			0.065
Delivery	19 (90.5%)	7 (63.6%)	
Abortion	2 (9.5%)	4 (36.4%)	
Cesarean delivery, n (%)	8 (38.1%)	6 (54.5%)	0.373
Trimester of abortion, n (%)			0.269
First trimester	1 (4.8%)	0 (0)	
Second trimester	1 (4.8%)	3 (27.3%)	
Third trimester	0 (0)	1 (9.1%)	
Weeks of gestation at delivery, weeks (range)	38 (30-41)	35.4 (31-40)	0.08
Fetal birth weight, grams (range)	3073 (2080-3820)	2500 (2070-3090)	**0.025***

IBD: Inflammatory Bowel Disease, CD: Crohn's Disease, HBI: Harvey-Bradshaw Index, TWI: Truelove-Witts modified Index, AntiTNF: Anti Tumour Necrosis Factor alpha.

Table 4. ***Inferential analysis of the variables with respect to the adherence group (Part 2).***

low birth weight children more frequently than patients with no activity or no IBD (OR: 1,39; 95%: 1,05-1,83).

The type of treatment of the patients at the time of conception, and its continuation during pregnancy, does not show differences between the groups adherent and non-adherent to the therapeutic plan (p= 0.631), nor does it seem to be related to worse conceptional outcomes as the most recent evidence shows today. Thiopurines, classically reviled and withdrawn from the therapeutic plan, have been shown to be safe during pregnancy, as demonstrated in the study published by Casanova *et al.*[29] where 187 pregnant women exposed to thiopurines were retrospectively analyzed and compared with a group of 318 non-exposed patients, without finding an increased risk of complications in pregnancy or in the newborn.

Aminosalicylates, including mesalazine and sulfasalazine, show a very high safety profile and there is ample evidence to support maintaining them throughout pregnancy[30].

Similarly, the review and meta-analysis carried out by Nielsen *et al.*[31] analyzing 48 studies and more than 6900 patients, concluded that Anti-TNF drugs (Adalimumab, Infliximab, Certolizumab and Golimumab), Anti-integrins (Vedolizumab) and Anti-Interleukins 12/23 (Ustekinumab), used in pregnancy, did not increase adverse events during pregnancy or in the newborn compared to the general population.

The use of corticosteroids (budesonide, prednisone, prednisolone) during pregnancy is framed within the control of the disease flare, recommending their use just long enough to control inflammatory activity. Results of the PIANO[32] study, which analyzed more than 1400 pregnancies, show that the offspring of mothers exposed to corticosteroids had more frequent preterm births, low birth weight or more intensive care admissions than the offspring of non-exposed mothers.

The use of antibiotics in IBD is usually limited to the treatment of perianal disease, pouchitis or abdominal sepsis, the most commonly used being cripofloxacin and metronidazole. The use of metronidazole is safe during pregnancy, according to the review published by Sheehy *et al*[33]. In contrast, ciprofloxacin is associated with musculoskeletal abnormalities in animals, and its use in the first trimester of pregnancy should be avoided despite data from a recent meta-analysis[34] that showed consistent data on the safety of its use in pregnancy.

The drugs to avoid during pregnancy are those that have demonstrated teratogenic potency or those for which there are still insufficient safety data in humans, being contraindicated by the ECCO clinical practice guideline during pregnancy and

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lactation: Methotrexate, Tofacitinib, Upadacitinib, Filgotinib and Ozanimod.

We would like to highlight the sample size and the retrospective nature of the study as its main limitations.

Conclusion

In our study we have found differences between groups in terms of the presence of flares and fetal birth weight, highlighting the importance of inflammatory activity on gestation. This importance is reinforced by the higher incidence of miscarriages in patients with mild-moderate inflammatory activity compared to patients in remission, where no pregnancy termination was recorded.

For all these reasons, both the data obtained in our study and those offered by the literature support the idea that it is not so important the type of treatment the patient is receiving before pregnancy, but rather that this treatment satisfactorily controls the activity of the disease. To this end, preconception counseling and the establishment of a therapeutic plan agreed upon with the patient should be a primary objective.

Montreal classification for Crohn's disease		
Age at diagnosis (A)	**Location (L)**	**Evolutionary pattern (B)**
A1: ≤ 16 years A2: 17-40 years A3: > 40 years	L1: ileal L2: colic L3: ileocolic L4: upper gastrointestinal	B1: inflammatory B2: obstructive/stenosing B3: fistulizing P: perianal disease
Montreal classification for ulcerative colitis		
Extent (E)	**Severity (S)**	
E1: ulcerative proctitis (limited to rectum, up to 15 cm, distal to rectosigmoid junction.	S0: clinical remission, asymptomatic.	
E2: left colitis (involvement distal to the splenic angle).	S1: Mild. ≤ 4 bowel movements per day with or without blood. No systemic symptoms (fever, tachycardia and/or anemia) and normal inflammatory markers. S2: Moderate. ≥ 5 stools per day with minimal systemic involvement.	
E3: extensive colitis (involvement proximal to the splenic angle).	S3: Severe. ≥6 bowel movements per day, tachycardia (>90 bpm), temperature greater than 37.5°, hemoglobin less than 10.5 g/100 ml and erythrocyte sedimentation rate > 30 mm/h.	

Anexe 1. ***Montreal Classification for Crohn's Disease and Ulcerative Colitis.***

Harvey-Bradshaw Index (HBI)		
Remission <5 Mild activity 5-7 Moderate activity 8-16 Severe activity >16	**General condition**	**Very good: 0 points** **Slightly bad: 1 points** **Bad: 2 points** **Fairly bad: 3 points** **Very bad: 4 points**
	Abdominal pain	**No: 0 points** **Mild: 1 points** **Moderate: 2 points** **Severe: 3 points**
	Number of bowel movements	**1 point per stool**
	Abdominal mass	**No : 0 points** **Doubtful: 1 point** **Definite: 2** **Definite and painful: 3**
	Complications	**Arthralgia, uveitis, erythema nodosum, oral aphthae, pyoderma gangrenosum, anal fissure, fistula, abscess: 1 point each**

Anexe 2. ***Activity Indices for Crohn's Disease (Harvey-Bradshaw).***

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Modified Truelove-Witts index (TWI) Inactive : <11; Mild activity 11-15; Moderate 16-21; Severe >21			
Score	**1 point**	**2 point**	**3 point**
No. of stools	<4	4-6	>6
Blood in stool	No	Mild	Moderate-Severe
Heart rate (bpm)	<80	80-100	>100
Temperature (°C)	<37°C	37-38°C	>38°C
Hemoglobin (g/L)	>12	10-12	<10
ESR (mm/h)	<15	15-30	>30
Leukocytes	<10.000	10-13000	>13000
Potassium	>3,8	3-3,8	<3
Albumin	>33	30-32	<30

Anexo 2. ***Ulcerative Colitis (modified Truelove-Witts).***

It is our role as physicians treating patients with IBD of gestational age to raise awareness of the importance of disease control, adherence to treatment and close follow-up during pregnancy.

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REVIEW ARTICLE

COLONOSCOPY PREPARATIONS: ELECTROLYTE IMBALANCES AND PRECAUTIONS IN THE FRAGILE PATIENTS.

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Abstract

Bowel preparation intake for colonoscopy can cause electrolyte imbalances. Although it is a rare complication, occurs as a consequence of the loss of electrolytes and water into the intestinal lumen, and because some electrolytes from the preparations can be absorbed. The possible imbalances cover all the alterations range of the internal environment (hypo and hypernatremia, hypo and hyperkalemia, metabolic acidosis, hypocalcaemia, and hyperphosphataemia or hypermagnesaemia). Electrolyte disturbances and their severity depend on electrolyte content of the preparation solution, the fluid replenishment conducted, and patient characteristics.

Electrolyte imbalances are generally transient, and these should not cause complications if adequate fluid replenishment with or without electrolytes during bowel preparation is conducted and maintained over time once the colonoscopy is performed. We reviewed the most frequent electrolyte imbalances that occur with the most used bowel cleansing preparations and precautions to be taken into consideration in fragile patients.

Keywords: colonoscopy, bowel preparations, hyponatremia, hypernatremia, hypermagnesaemia.

Introduction

Colonoscopy is one of the most frequently used medical procedures. It is considered the Gold-standard technique for colorectal cancer (CRC) screening, as well as for the removal of adenomatous polyps with precancerous potential[1,2]. Colonoscopy is estimated to reduce CRC incidence by 40% and mortality by 60%[3].

The diagnostic effectiveness of this technique depends on good bowel cleansing, so the use of bowel preparations is essential. Inadequate cleansing has a detrimental effect on all aspects of the colonoscopy procedure, leading to significantly lower rates of adenoma detection[4], failure of cecal intubation, increased operative time and associated complications, and the need for repeat procedures. In summary, higher healthcare costs[2,5].

The ideal preparation should achieve excellent cleanliness allowing visualisation of the entire colonic mucosa without the need to remove residues during the examination. It should also be safe for the patients, with good tolerability and easy compliance[6].

The most commonly used preparations for colonoscopy are 4-litre polyethylene glycol (PEG), PEG + 2-litre ascorbic

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acid, PEG + 1-litre ascorbic acid and sodium picosulphate + magnesium sulphate (PCM)[5]. This availability of different bowel cleansing preparations, both in composition and volume, makes it possible to choose the most appropriate one for each patient according to their specific characteristics and comorbidities[5]. Thus, iso-osmotic bowel preparations contain an iso-osmotic liquid and a non-absorbable polymer (PEG) that causes the ingested liquid to be retained in the lumen of the colon. These preparations are considered safer for patients at risk of water and electrolyte disturbances, as they do not cause significant electrolyte or water changes. On the other hand, hyperosmotic bowel preparations provide a large amount of osmotically active molecules with a smaller volume of fluids. The ingested osmoles draw fluid into the colon and stimulate evacuation. However, this fluid exchange process can result in intravascular volume contraction and electrolyte disturbances[2,5].

The main colonoscopy preparations have been shown to provide adequate bowel cleansing safely in healthy individuals without significant comorbidity[6]. However, occasionally disturbances are described as a consequence of water and electrolyte loss through the intestinal lumen, or absorption of some of the electrolytes contained in the preparations. Thus, the possibilities cover almost the entire spectrum of alterations of the internal environment (hypo- and hypernatraemia, hypo- and hyperkalaemia, metabolic acidosis, hypocalcaemia and hyperphosphataemia or hypermagnesaemia)[7,8].

The possibility of suffering these alterations and their severity will depend on the electrolyte content of the preparation, the type of replenishment performed and the characteristics of the patient. Generally, these are transitory alterations that, with adequate fluid replacement with or without electrolytes during the bowel preparation, and maintained over time once the colonoscopy has been performed, should not cause problems[7].

The risk is particularly high in certain population groups. This is the case, for example, in the elderly, who have an altered thirst mechanism and in whom it is necessary to insist on fluid intake to obtain adequate replacement. Also in patients with nephropathies or under diuretic treatment whose ability to concentrate urine is impaired. Patients with heart failure or cirrhosis of the liver, who not only have electrolyte disturbances and volume overload, but are also more vulnerable to changes in ion concentrations, with a higher incidence of arrhythmias. Finally, mention should be made of patients being treated with insulin or with drugs that may affect water-electrolyte balance (NSAIDs, ACE/ARB II, diuretics, corticosteroids) or make them more vulnerable to these imbalances (cardiac glycosides, carbamazepine, etc.)[7,8].

This article reviews the most frequent hydroelectrolyte alterations (hyponatraemia, hypernatraemia and hypermagnesaemia) that may occur with the most commonly used intestinal cleansing preparations in Spain (PEG and PCM-based solutions[5]) and the precautions to be considered in fragile patients.

Alterations in plasma sodium concentration

Both hyponatraemia and hypernatraemia are disorders that reflect alterations in plasma sodium concentration ([Na]), i.e. disorders in the regulation of water and not of a greater or lesser total amount of sodium. The fundamental premise for the correct management of these disorders is to remember that [Na] is a reflection of the osmolality of the extracellular fluid. Changes in osmolality imply changes in the amount of water, whereas a change in the total amount of sodium determines the total amount of extracellular fluid and implies changes in volume[9].

Hyponathremia

Hyponatraemia ([Na] <135mmol/l) is a relatively common condition in hospitalised patients, with an incidence and prevalence in adults of 1 and 2.5%, respectively. Its occurrence implies that there is a gain of free water, either due to excessive water intake (oral or parenteral) or due to renal difficulty in excreting it[10].

Symptoms (apathy/agitation, fatigue, anorexia, nausea, headache, muscle cramps, tachycardia, oliguria/anuria and confusion) appear with [Na] <120-125 mmol/L. If [Na] values <110/115 mmol/L are reached, the patient may experience convulsions, coma and shock[9].

Intake of large volumes of water, especially in patients with reduced free water clearance, predisposes to the development of hyponatraemia[6]. In the colonoscopy setting, after taking the bowel cleansing preparation, this imbalance may occur as a consequence of intravascular volume depletion (mainly due to diarrhoea) and subsequent excessive thirst, or due to abundant water intake in a short time together with the bowel preparation agent and low solute intake. It may also occur as a consequence of difficulty in eliminating free water and increased antidiuretic hormone release, which during bowel preparation may be triggered by nausea, pain or anxiety[7].

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PCM based preparation has been associated with hyponatraemia in patients with no risk factors for sodium concentration abnormalities[7]. Severe cases of hyponatraemia have even been reported with PCM as a consequence of intravascular volume depletion (Table 1)[11-23]. A retrospective study found a higher risk of hospital admission for hyponatraemia in patients >65 years prepared with PCM than with PEG preparations[5,12].

In the case of PEG-based solutions, the occurrence of hyponatraemia has been associated with the syndrome of inappropriate antidiuretic hormone secretion. Several cases of hyponatraemia have also been reported with the 4L PEG preparation following excessive water intake in a short period of time[6,24-27].

Hyponatraemia may have more severe consequences when it develops rapidly (<48 hours), or in patients with individual susceptibility or underlying neurological disease. It is therefore advisable to counsel patients and instruct them that replacement fluids should be isotonic solutions, avoiding drinking only water or hypotonic beverages which may lead to electrolyte imbalance.

Hypernatremia

Hypernatraemia ([Na] >145 mmol/L) is less common than hyponatraemia and usually occurs as a result of water loss or, more rarely, sodium gain(10). When a small rise in sodium occurs, the body stimulates the thirst centre and the release of antidiuretic hormone (ADH). Thirst is paramount as even maximal ADH secretion may fail to retain enough water to compensate for losses. Thus, thirst provides the ultimate protection against hypernatraemia and it is very difficult for hypernatraemia to exceed 150 mmol/L [Na] in adults without consciousness deficits, with normal thirst mechanism and/or free access to water[9,28]. When hypernatraemia due to water loss occurs, it is usually in patients with hypodipsia or, more commonly, in adults with altered mental status or without access to water[10].

Symptoms that may occur include weakness, somnolence, confusion and convulsions. The manifestation of these symptoms depends on how quickly hypernatraemia has developed, but they are unlikely at [Na] below 155 mmol/L[28]. Symptoms of central nervous system dehydration (thirst, dry skin and mucous membranes, weight loss, confusion, hallucinations and coma) appear at [Na] >160 mmol/L[28].

Isoosmotic preparations themselves do not affect [Na], but in patients with impaired renal water management or in elderly patients with decreased thirst there is a risk of hypernatraemia. For example, severe hypernatraemia with acute kidney injury (in the range of 166 mEq/L) has been reported with oral sodium phosphate (SP) preparations in elderly patients with poor water intake[29-30]. In fact, the ESGE (European Society of Gastrointestinal Endoscopy) guideline does not recommend the use of FS for routine bowel preparation[5].

PEG-based preparations contain added electrolytes to create iso-osmotic solutions. They are absorbed to a minimal extent in the intestine, even if the mucosa is not intact (e.g. in patients with inflammatory bowel disease)[5]. They are also considered safe in patients at risk of water-electrolyte disorders, as they do not cause significant electrolyte or water exchange across the colon wall[5].

With high-volume (4L) PEG solutions, studies have shown no significant alterations in vital or electrolyte parameters[5].

In the case of very low volume (1L) PEG preparations, the electrolytes present in the formulation, together with additional intake of clear fluids, prevent clinically significant changes in sodium, potassium or water levels. However, mild and transient hypernatraemia of no clinical significance has been reported in both trials and clinical practice[31-34]. A study evaluating renal function in patients hospitalised after bowel preparation with PEG 1L or PEG 4L did not observe significant electrolyte alterations, neither in renal function nor in hydration as assessed by haematocrit[35]. Finally, no clinical events attributable to electrolyte imbalance or dehydration were observed in patients >65 years of age[36-37].

Among the recommendations, good hydration should always be ensured in accordance with the losses and the patient's pathology. It is important to note that the replenishment process does not end at the time of colonoscopy, but should be maintained until the following day. In patients prepared with very low volume PEG (1L), this replenishment should be done with free water, avoiding isotonic drinks. Finally, in patients at risk, as well as in those with vomiting during the preparation and/or who have not followed adequate hydration guidelines, special monitoring of electrolyte levels should be carried out before and after treatment.

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Reference	Gender	Age (years)	Symptoms	Sodium levels (mmol/L)	Preparation
(14)	Female	76	Loss of consciousness and seizures	112	SPMS
(15)	Female	64	Seizures	111	SPMS
(15)	Female	75	Seizures	116	Phosphosode + Bisacodyl
(15)	Female	27	Seizures	132	Phosphosode + Bisacodyl
(16)	Female	65	Nausea and vomiting	124	SPMS
(16)	Female	74	Acute confusion	120	SPMS
(16)	Female	73	Seizures tonic-clonic	115	SPMS
(17)	Female	80	Acute confusion and generalized seizures	110	SPMS
(18)	Female	57	Seizures tonic-clonic	120	SPMS + Bisacodyl
(19)	Female	78	Disorientation and dizziness	108	SPMS
(20)	Female	64	Coma	111	SPMS
(20)	Female	69	Dysarthria and paresthesia in upper limbs	128	SPMS
(21)	Male	48	Coma	110	SPMS
(22)	Female	61	Encephalopathy	122	SPMS
(23)	Female	62	Convulsiones	119	SPMS
(24)	Female	59	Seizures	120	PEG 4L
(25)	Female	73	Seizures tonic-clonic	117	Gatorade 2L mixed with 225 g of PEG3350 (Miralax)
(26)	Female	64	Weakness in lower limbs	118	PEG 4L
(27)	Female	70	Seizures tonic-clonic	110	PEG 4L +3L Water
(27)	Female	65	Seizures tonic-clonic	127	PEG 4L

PEG: polyethylene glycol; SPMS: sodium picosulfate + magnesium sulfate.

Figure 1. ***Characteristics and presentation of patients with symptomatic hyponatraemia related to bowel preparations reported in the literature.***

Hypermagnesaemia

Various preparations containing PCM may cause a transient increase in serum magnesium levels[6].

Due to their hyperosmolarity and magnesium content, these solutions are contraindicated in some patients. For example, those with congestive heart failure, hypermagnesaemia, rhabdomyolysis, gastrointestinal ulcers or in patients with severely impaired renal function who may suffer from magnesium toxicity (as the kidney is primarily responsible for magnesium elimination)[5,7].

Magnesium-free preparations do not confer an increased risk of hypermagnesaemia[7].

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Conclusions

After preparation with hyperosmotic solutions, fluid replacement should always be done with electrolyte solutions, avoiding free water or hypotonic drinks.

After preparation with iso-osmotic solutions, fluid replacement should be done with free water or hypotonic beverages.

In patients in whom any preparation regimen carries a risk of dehydration and/or possible electrolyte imbalances (even caused by vomiting alone), hyperosmotic preparations may further increase these risks[5].

PCM-based preparations should be used with caution in patients at risk (congestive heart failure, liver cirrhosis or hepatic failure with ascites, chronic kidney disease, etc.) or suffering from hypovolaemia (such as patients taking high doses of diuretics)[2,5-8].

Isoosmotic solutions are safer options in patients with relevant comorbidities or treated with medications that influence water and electrolyte balance[2,5-8].

In elderly patients, osmotically balanced PEG-based solutions are the preparations of choice as they are considered the safest[2,5-8].

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REVIEW ARTICLE

INTESTINAL ULTRASOUND: IS IT TIME TO JOIN OUR IBD UNITS? HOW DO WE DO IT?

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Abstract

The objective in the treatment of inflammatory bowel disease is to achieve early control of the disease with the intention of obtaining mucosal and even transmural healing.

To do this, it is necessary to have monitoring techniques that allow us to closely monitor the evolution of the disease.

Intestinal ultrasound is a good alternative to more invasive imaging techniques, with similar precision.

It is quickly and easily available, provides real-time response and allows early clinical decision-making, being able to modify the therapeutic and monitoring strategy of patients.

The incorporation of ultrasound in IBD units allows us to save time and resources for the benefit of the patient themselves.

Keywords: intestinal ultrasound.

Introduction

The diagnosis of Crohn's disease (CD) and ulcerative colitis (UC) is based on a combination of clinical, analytical, endoscopic, radiological and histological criteria[1]. We know that it is important to achieve early control of the disease with the intention of achieving mucosal and even transmural healing.

Effective and reproducible monitoring techniques are needed to allow us to closely follow the evolution of the disease. Colonoscopy is a fundamental technique in the management of this disease and is considered the "gold standard" for the diagnosis of UC. However, for patients with CD, endoscopy does not assess transmural or proximal involvement. Furthermore, in up to 20% of cases, colonoscopy is incomplete due to the severity of the disease or the presence of strictures[2]. For this reason, we need to resort to imaging techniques such as intestinal ultrasound, CT and entero-MRI.

In general, both the consensus documents of the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU)[3], the European Crohn's Disease and

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Colitis Organisation (ECCO) and the European Society of Gastrointestinal and Abdominal Radiology (ESGAR)[1] consider that both intestinal ultrasound and abdominal CT and MRI have comparable diagnostic accuracy for the initial evaluation of CD, disease severity and assessment of activity and detection of its main complications, strictures, fistulas and abscesses.

Advantages and limitations

The advantages of intestinal ultrasound are:

- It is cheap, cost-effective, accessible and widely available.

- It is the best tolerated test by patients.

- It is non-invasive and harmless.

- It does not require preparation. Although fasting for 4-6 hours is recommended, in general it does not interfere too much with the technique, with the exception of Doppler, which can be artefactual due to the lack of fasting.

- It can be repeated as many times as necessary.

- It provides immediate results.

In addition to the aforementioned advantages, intestinal ultrasound has an additional feature that makes it an unbeatable technique for monitoring IBD, and that is the possibility of performing it during a medical consultation. This is what is known in the literature as POCUS (Point of Care Ultrasonography)[2,3].

This aspect makes it possible to stratify patients during the consultation, optimise resources by reducing the need for MRI and colonoscopy, speed up decision-making and strengthen the doctor-patient relationship.

Among the limitations, we highlight the following:

- Operator dependent. The learning curve depends mainly on previous experience in abdominal ultrasound.

- It depends on the quality of the ultrasound machine and probes. Conventional 3-5 MHz probes are necessary for an initial general abdominal exploration, but for a detailed exploration of the intestinal loops it is essential to use high frequency probes (5-15 MHz), flat or miniconvex, as they allow a higher resolution assessment of the intestinal wall.

- Patient's constitution. Obesity is the fundamental limiting factor[3].

- Quantification of the extent. MRI quantifies more precisely the extent of involvement in cases of extensive disease.

- Sensitivity depends on the location. Ultrasound may have limitations in the assessment of the rectum, sections of the proximal intestine (jejunum) and the deep pelvis[3].

Ultrasound findings in Crohn's disease

The main ultrasound findings in relation to Crohn's disease include wall thickening, colour Doppler hyperemia, loss of layered structure, ulcers, fibro-fatty proliferation and adenopathy.

1. **Wall thickening:** this is considered the key parameter for diagnosis and assessment of activity, with the advantage of low inter-observer variability. There is usually an increase in the thickness of the submucosa (hyperechogenic) over the other layers. The measurement should be made in a longitudinal section, over the anterior wall of the loop and avoiding mucosal folds. The cut-off point is ≥ 3 mm or ≥ 4 mm if high specificity is preferred (S 89.7%, E 95.6% vs S 89%, E 96% respectively). The EFSUMB (European Federation of Societies for Ultrasound in Medicine and Biology) recommends using a cut-off point of 3 mm for higher sensitivity in diagnosis and activity assessment. It is usually accompanied by loop stiffness and loss of peristalsis[2].

2. **Wall hyperemia:** hyperemia identified by colour Doppler is another parameter of activity. It is assessed using Limberg's modified semi-quantitative scale that ranks vascularity from 0 (no vascularity) to 3 (intense vascularity) (Figure 2). It has shown a good correlation with histological findings and with clinical and endoscopic activity. A grade 2-3 showed a specificity of over 90% for severe endoscopic disease and a positive predictive value of 97% for the presence of ulcers on endoscopy.

3. **Loss of layered structure:** high-frequency probes allow exploration of the layered structure of the intestinal wall and identify loss of this structure which may be focal, usually secondary to ulcers, or

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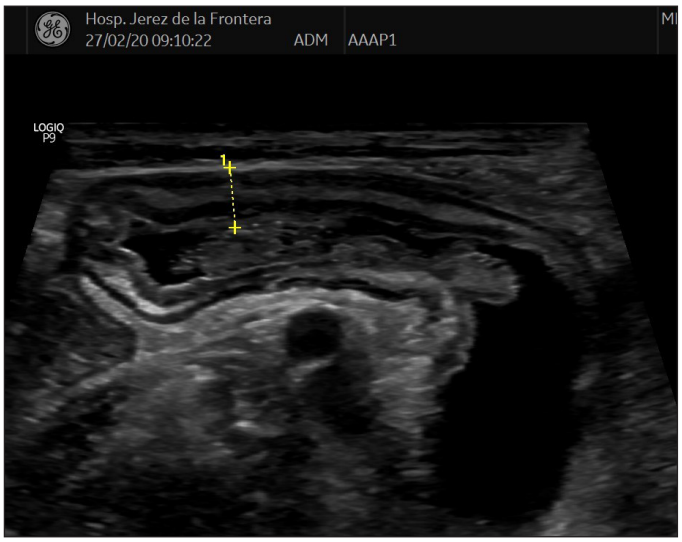

Figure 1. ***Crohn's disease. Wall thickening of 5.94 mm and preservation of the layered structure. The thickening is due to the expense of the mucosal and submucosal layers.***

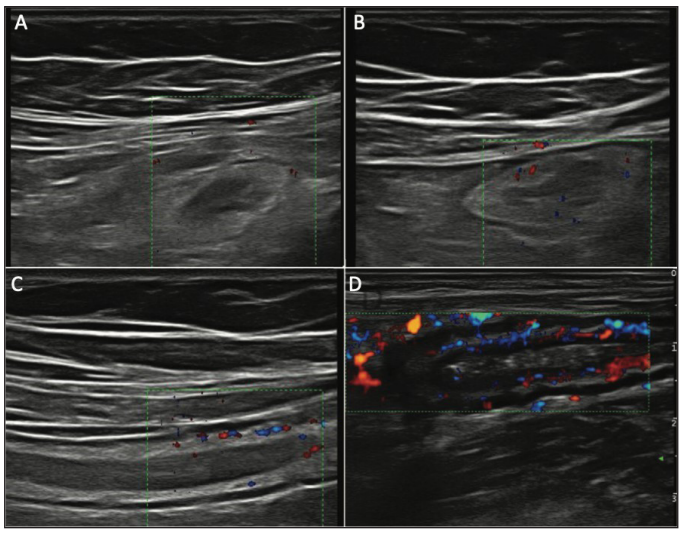

Figure 2. ***LIMBERG score: A) Grade 0: no vessels; B) Grade 1 or barely visible: 1-2 points/cm2; C) Grade 2 or moderate: 3-5 points/cm2; D) Grade 3 or intense: >5 points/cm2 or even vessels outside the wall. Image by Muñoz F et al[3].***

segmental. However, it can sometimes be seen in very advanced latent disease, especially of the left colon, due to severe fibrosis. A correlation has been established with endoscopic activity and increased risk of surgery[4,5].

4. **Fibro-fatty proliferation:** another ultrasound parameter commonly associated with active CD is mesenteric fat involvement. It is characterised by a homogeneous increase in the echogenicity of the fat surrounding a segment affected by the disease. It is associated with wall thickening and fistulas. It may persist in patients in remission[6].

5. **Adenopathies:** can be identified in up to 25% of patients with CD, being more frequent in childhood, at diagnosis and in patients with fistulas and abscesses, but are of limited value in assessing disease activity. They usually respond to treatment[2,7].

Transmural complications

In general the performance of ultrasound is similar to CT or MRI, taking into account the limitation of ultrasound in the assessment of the deep pelvis. The use of oral or intravenous contrast agents may be particularly useful in this clinical context:

- **Oral contrast:** oral intake of a variable volume (250-800 ml) of an isotonic contrast solution (polyethylene glycol) to distend the loops. Studies using this technique, known as SICUS (small intestine contrast ultrasonography), show a significant contrast ultrasonography), show an increased ability to assess the proximal small bowel, detect strictures and assess postoperative recurrence, as well as reduce interobserver variability. A drawback of this technique is that the duration of the procedure increases from 25 to 45-60 min and complicates the assessment in colour Doppler mode[3].

- **Intravenous contrast:** the most commonly used ultrasound contrast is SonoVue®, composed of sulphur hexafluoride microbubbles. It is completely intravascular, does not pass into the interstitium, is eliminated via the respiratory tract and has an excellent safety profile. It increases sensitivity in the detection of bowel wall vascularisation compared to the colour Doppler study. It allows the assessment of microvascularisation, whereas Doppler assesses macroscopic vessels[8].

It is necessary to have specific software installed on the ultrasound machine.

There is great variability in the measurements obtained with intravenous contrast from one device to another, so it is recommended, as far as possible, to use the same ultrasound scanner and transducer for monitoring the patient[3].

IV contrast allows us to:

- **Visualise the sections of intestinal** wall that are inflamed.

- **To help differentiate between inflammatory and fibrotic stenosis.**

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-**Differentiate between abscesses and phlegmonous areas**.

Transmural complications include inflammatory masses (phlegmon and abscesses), fistulas and strictures.

- **Phlegmons/abscesses:** abscesses appear as hypoechoic or anechoic masses with posterior reinforcement and well-defined thick walls that may contain gas, while phlegmons appear as hypoechoic masses with poorly defined margins and no identifiable wall. Sometimes their differentiation on B-mode ultrasound is complicated.

The use of intravenous contrast can reliably differentiate them, as phlegmon shows a diffuse enhancement of the lesion while abscesses show peripheral enhancement and an avascular central portion. The use of contrast improves the specificity of the diagnosis of abscess and more accurately defines its size, which may be important in deciding whether the collection requires drainage[9].

- **Fistulas:** these are identified on ultrasound as hypoechoic tracts extending from the loops to other intestinal segments or other organs, although if they are gassy they may show echogenic foci with or without movement within the tract. The sensitivity of ultrasound in the diagnosis of fistulas is 67%-87%, similar to that of CT or MRI, with a specificity of 90-100%[3].

- **Stenosis:** Several systematic reviews and consensus documents state that ultrasound, CT and MRI have high sensitivity and specificity for the diagnosis of small bowel and colon stenosis, with similar diagnostic yield[10,11]. In a recently published systematic review the sensitivity of ultrasound was 80% (95% CI, 75.2%-84.2%) and the specificity 95% (95% CI, 89.7%-99.8%)[12]. The use of oral contrast (SICUS) significantly improves the sensitivity of the technique for the diagnosis of low-grade stenosis[13].

According to a recently published consensus document, a stricture can be defined as a thickened (>4 mm), rigid, narrow lumen segment followed by a distended bowel segment anterior to the segment[14].

With oral contrast it is defined when the lumen of the affected bowel segment has a diameter of less than 1 cm, measured at maximum loop distension[15].

Indications for ultrasound in IBD

Intestinal ultrasound plays a key role in the initial diagnosis and follow-up of inflammatory bowel disease, with high sensitivity and specificity in the suspicion of Crohn's disease, in the detection of inflammatory activity and allows early diagnosis of intra-abdominal complications such as strictures, fistulas and abscesses; it has also proven useful in the monitoring of treatment and in post-surgical recurrence.

The ECCO consensus puts MRI and ultrasound at the same level in the initial diagnosis of CD, in the monitoring of treatment, in the monitoring of the asymptomatic patient, and in the detection of complications, although when it comes to abscesses or fistulas located in the pelvis, MRI probably has an advantage. In monitoring cholic involvement and recurrence, colonoscopy would be the choice, although ultrasound could be sparing[1].

Ultrasound monitoring of Crohn's disease

We have seen how ultrasound is useful in the diagnosis of CD, in assessing the extent of the affected area and in detecting complications, but to determine whether it is useful in monitoring the disease, it must be able to detect changes with treatment, quantify them and ensure that the findings are of prognostic interest to allow us to justify treatment adjustments.

Among the studies assessing the usefulness of this technique in the monitoring of CD, the study by Ripollés et al (16), which included 51 patients with CD treated with anti-TNF and followed prospectively for 52 weeks, stands out. They observed that 85% of the patients showed an improvement in ultrasound parameters as early as week 12 and that this predicted the results at week 52. Only 11% of patients with improved ultrasound parameters required intensification or surgery compared to 65% of those who did not experience early improvement.

Which ultrasound parameters change with treatment?

Initial response assessment (with ultrasound or MRI) is recommended within the first 6 months after treatment initiation. The main study demonstrating the usefulness of ultrasound in CD monitoring is the multicentre, prospective TRUST study[17], which followed 234 active patients after treatment for 12 months. Virtually all parameters assessed (thickness, loss of stratification, fibrofatty proliferation, Doppler signal, adenopathy or stenosis) showed improvement by the third month of treatment. Ultrasound changes to assess response may be even earlier, having already been described in ultrasound examinations at 2 or 4 weeks after the start of treatment. In this study, the probability of achieving normal ultrasound parameters was 58%, considerably higher than in

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previous studies, but less likely in the ileum than in the colon segments.

Can we quantify these changes?

There are different ultrasound indices, but one of the limitations is the lack of quantitative indices that are correctly validated and simple to apply, unlike what happens with MRI (18). Recently, at least three validated indices have been published, including wall thickness and Doppler signal as main variables to try to reduce inter-observer variability.

Does ultrasound change the management of CD?

Ultrasound is a technique that aids in the monitoring of CD and, due to its immediacy, allows decisions to be made immediately on the spot, saving time and resources.

In the study by Novak *et al*[19], clinical, biological and endoscopic information from 49 patients with CD is provided to two physicians who make a decision on the approach to be taken.

Subsequently, after providing the ultrasound findings, both physicians changed the approach in 60 % of the patients, either therapeutically or by performing other examinations. It should be noted that the ultrasound scan in this study was performed in the consultation room or POCUS itself, so that the change of attitude was made at the same time as the patient was assessed, without waiting.

Therefore, ideally, ultrasound will be scheduled in asymptomatic patients or for treatment monitoring, but in symptomatic patients or those with clearly elevated biomarkers, POCUS or on-the-fly ultrasound would be ideal.

Usefulness of ultrasound in post-surgical recurrence

A particular monitoring situation is recurrence after surgery. In this situation colonoscopy and calprotectin levels are the methods with the highest diagnostic yield, but ultrasound can be a supportive technique. In the meta-analysis by Rispo *et al*[20] including 536 patients in 10 studies, the sensitivity of ultrasound in detecting recurrence was 94%, with a specificity of 84%. Specificity is lower, 88%, in mild recurrence (Rutgeerts Index i1-i2), and increases to 97.7% in severe recurrence (Rutgeerts Index i3-i4).

Wall thickness > 3 mm has been found to correlate with a mild Rutgeerts Index (i1-i2) and wall thickness greater than 5.5 mm usually corresponds to a more severe Rutgeerts Index (i3-i4), and thus colonoscopy can sometimes be avoided.

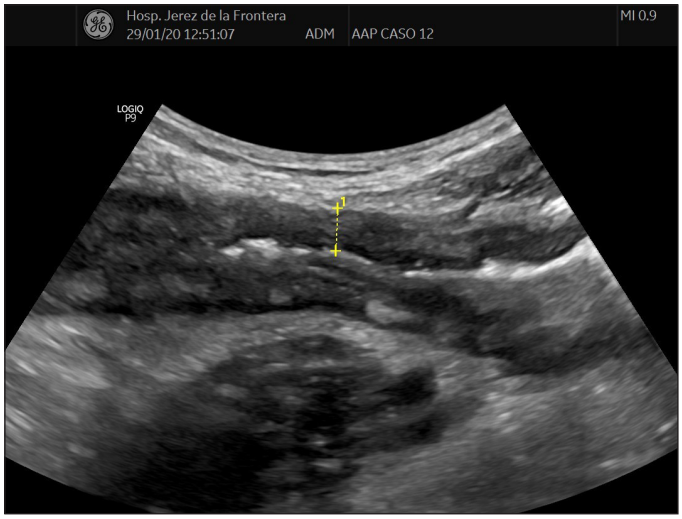

Figure 3. ***Crohn's disease. Segment of the ileum of a patient with CD with marked inflammatory activity. Focal alteration of the layered structure is observed.***

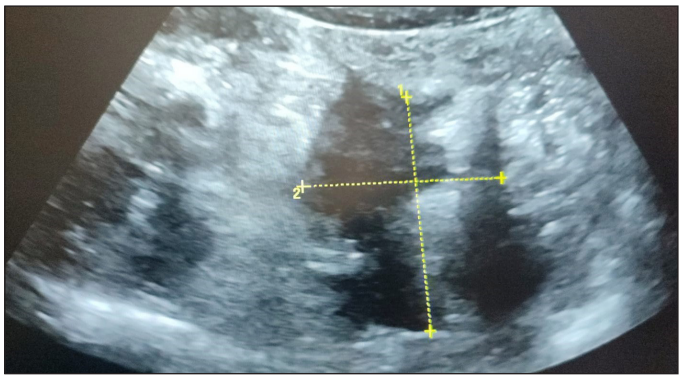

Figure 4. ***Crohn's disease. Interasal area, with poorly demarcated margins of about 3.9 x 4 cm with isoechoic and other anechoic areas that may be an inflammatory plastron without being able to rule out abscessation without performing ultrasound contrast.***

Treatment objective: mucosal healing vs. parietal healing.

The treatment objective is becoming more and more demanding. Years ago the aim was to keep the patient free of symptoms, then we added the normalisation of biomarkers and nowadays the objective is to achieve mucosal healing and, if possible, also parietal healing.

In order to standardise the ultrasound targets to be achieved, a consensus has recently been published stating that parietal healing would be defined as a wall thickness of 3 mm or less together with no Doppler signal, while ultrasound response includes one of the following criteria: 2 mm reduction in thickness from baseline, 1 mm reduction together with a

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decrease in Doppler signal of at least 1 degree, or a reduction in thickness of more than 25%[21].

How and when to assess parietal healing?

Both entero-MRI and intestinal ultrasound are appropriate techniques to assess parietal response and healing.

It should be assessed 3-6 months after the start of treatment.

Should it be a therapeutic target?

It is not currently considered a formal therapeutic objective although it should be considered especially in patients with an inflammatory pattern, shorter time of evolution (< 2 years) and with lower wall thickness at the start of treatment (probably less than 5 mm).

Does it have prognostic value?

The prognostic value of parietal healing is superior to mucosal healing in important aspects such as the need for hospitalisation, surgery and therapeutic escalation, although it cannot be achieved in all patients and it must be selected in which group of patients we can achieve it.

As an example, in the study by Castiglione *et al*[22]the probability of hospitalisation, surgery or recurrence is significantly higher in patients who achieved mucosal healing but with persistent lesions on ultrasound than in those with parietal healing.

Rather than achieving mucosal or parietal healing, it is likely to be a combination of both as the prognosis would still be better.

Usefulness of ultrasound in ulcerative colitis

In UC, the burden of monitoring falls on biomarkers, especially faecal calprotectin and colonoscopy, but ultrasound has a relevant supportive role. The role of ultrasound in UC monitoring is analysed in the TRUST&CU study[23] which includes 224 patients with UC followed prospectively with ultrasound at baseline and at weeks 2, 6 and 12 after initiation of treatment. At week 2 they already found a significant decrease in all parameters analysed. In addition, sigmoid wall thickness at week 2 predicted response to treatment at week 12.

Ultrasound findings in UC are similar to those described in CD, i.e. increased wall thickness, loss of layered stratification, hyperemia, etc., perhaps pointing out the loss of haustration as a characteristic of cholic involvement.

The main limitation of ultrasound in UC is the assessment of the rectum, which is especially relevant when this is the most affected area or when the disease is limited to this location.

Therefore, ultrasound in UC allows us to make a complementary assessment to the clinical and biomarkers, allowing us to have more information for making decisions on treatment or indication of other examinations such as colonoscopy. It also allows us to assess the extent of the disease in situations where colonoscopy has been incomplete due to stenosis, poor preparation or is not recommended due to the severity of the outbreak. And it appears to have a possible role in severe UC flare-ups in predicting response to treatment.

The study by Ilvemark *et al*[24] included 56 patients with severe UC flare-up who underwent baseline ultrasound at 24-72 hours and found that a decrease of 20% or more in baseline thickness was associated with a favourable response to intravenous corticosteroids, with a sensitivity of 84.2% and a specificity of 78.4%.

Conclusions

Intestinal ultrasound is a good alternative to more invasive imaging techniques, with similar accuracy.

In addition to being fast and readily available, it provides real-time feedback and enables early clinical decision making.

The use of POCUS can modify the therapeutic and follow-up strategy in up to 60% of patients with CD.

It can be used to assess and monitor disease activity and treatment response in UC.

Further studies are needed to develop reliable and reproducible activity indices, using colonoscopy and MRI as reference standards.

Intestinal ultrasound: Is it time to incorporate it into our IBD units?

It is highly advisable to incorporate ultrasound into IBD units and consultations, but this requires adequate logistical resources and even more necessary to be able to dedicate time to it. We cannot forget that with POCUS three acts are performed in one (consultation, intestinal ultrasound and review), saving time and resources for the benefit of the patient.

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CHRONIC DIARRHEA SECONDARY TO INTESTINAL SPIROCHETOSIS, SHOULD WE THINK ABOUT IT?

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Abstract

Human intestinal spirochetosis (HIS) is defined as a colonization of the apical membrane of the colonic mucosa and the appendix by spirochetes. It is a very rare finding, being more common in some populations (individuals living in villages and peri-urban environments in developing countries, recent immigrants from developing countries, men who have sex with other men and HIV positive patients), but the spirochete rarely is investigated as human enteric potential microorganism.

It is a slow-growing microorganism and has specialized growth requirements, which is why it is not detectable in human fecal samples using routine diagnostic methods. However, it has been histologically identified attached to the colon and rectum in patients with conditions such as chronic diarrhea, rectal bleeding, and/or nonspecific abdominal discomfort.

In this article we present the case of a patient with chronic diarrhea secondary to intestinal spirochetosis, highlighting the importance of considering this etiology in the differential diagnosis.

Keywords: chronic diarrhea, spirochetosis, brachyspira.

Introduction

Human intestinal spirochetosis (HIS) is defined as a colonisation of the apical membrane of the colonic mucosa and appendix by spirochetes, anaerobic filamentous bacteria[1].

It was first described by Harland & Lee in 1967. In humans, it has been associated with two species of spirochetes, *Brachyspira pilosicoli* (mainly asymptomatic, but sometimes as an opportunistic pathogen) and Brachyspira aalborgi (which may be pathogenic in humans more frequently than *B. pilosicoli*)[2,3] They must be distinguished from the family Spirocochaetaceae (genus Treponema, Borrelia, Spirochaeta) and Leptospiraceateae (genus Leptospiraceae) which are not associated with HIS and which induce completely different pathological processes.

It is a very rare finding in our environment with a higher prevalence in less developed countries, above 40% in men who have sex with men and also in patients positive for human immunodeficiency virus (HIV)[4]. In Europe, there is an estimated prevalence of 2.5-9%[2]. Increased prevalence has also been reported in areas of poverty, in critically ill patients with multiple organ failure, and in coexistence with gonococcal infection[5]. Although the mechanism of transmission is not fully

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understood, it is suggested that faecal-oral transmission is most commonly implicated, followed by sexual transmission.

It is slow-growing and has specialised growth requirements, so it is not detectable in human faecal samples using routine diagnostic methods. However, it has been identified histologically attached to the colon and rectum in patients with conditions such as chronic diarrhoea, rectal bleeding and/or non-specific abdominal discomfort.

In this article we present the case of a patient with chronic diarrhoea secondary to intestinal spirochetosis, highlighting the importance of considering this aetiology among the differential diagnoses. understood, it is suggested that faecal-oral transmission is most commonly implicated, followed by sexual transmission.

It is slow-growing and has specialised growth requirements, so it is not detectable in human faecal samples using routine diagnostic methods. However, it has been identified histologically attached to the colon and rectum in patients with conditions such as chronic diarrhoea, rectal bleeding and/or non-specific abdominal discomfort.

In this article we present the case of a patient with chronic diarrhoea secondary to intestinal spirochetosis, highlighting the importance of considering this aetiology among the differential diagnoses.

Clinical Case

We present the case of a 57-year-old patient under study in the Digestive Department for diarrhoea of 5-6 liquid or soft stools without pathological products per day, of one year's duration. As personal history, the patient is being treated with enalapril and simvastatin for hypertension and dyslipidaemia. She has no family history of interest. She denies toxic habits. Native of Spain, she denies recent trips to developing countries. She had previously had sexual relations with only one stable partner, none in the last 5 years.

An analysis was performed with blood tests showing mild iron deficiency (IST 12%) without anaemia (Hb 12.4 g/dl) and stool analysis with stool culture, parasites and *Cl. Difficile* negative, with high levels of calprotectin (303 µg/g of stool). Subsequently, a colonoscopy was carried out which revealed multiple aphthous ulcers in the right colon up to the hepatic angle suggestive of non-specific aphthous colitis (infectious or inflammatory) and multiple biopsies were taken (Figure 1). Pathological anatomy showed active chronic colitis of infectious aetiology with the presence of filamentous microorganisms attached to the colonic mucosa compatible with intestinal spirochetosis (Figures 2 and 3).

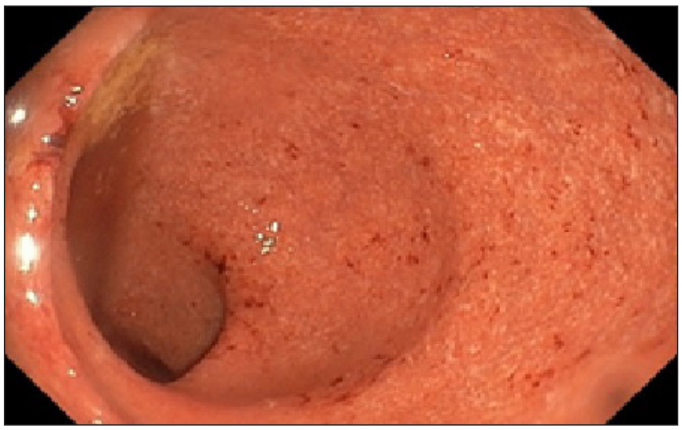

Figure 1. ***Colonoscopy. Multiple aphthous lesions were identified in the right colon.***

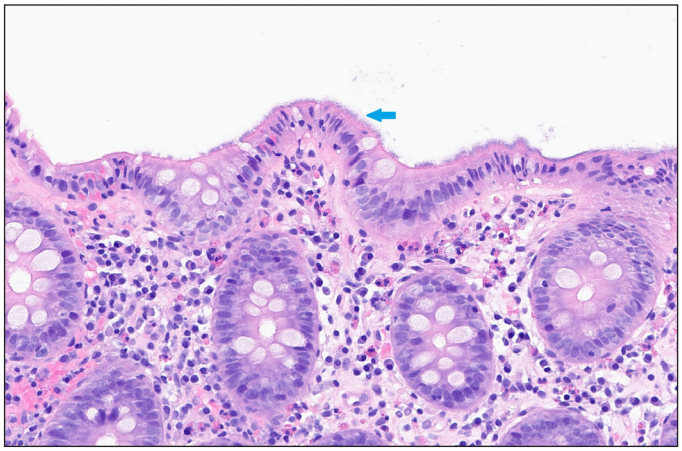

Figure 2. ***Haematoxylin-Eosin stain 40x. Colon mucosa showing a "false epithelial barrier" (blue arrow) at the brush border of the intestinal mucosa.***

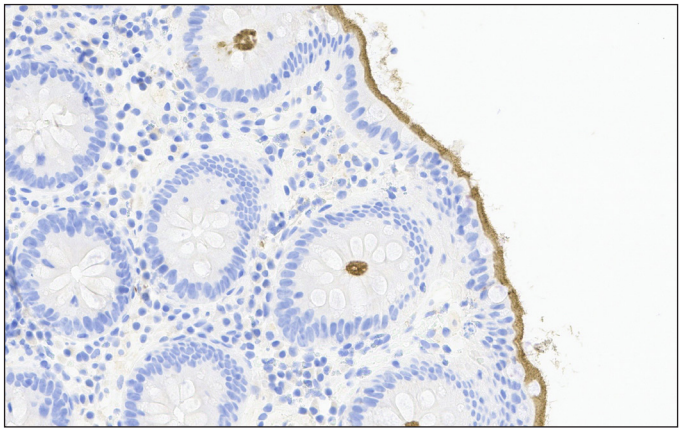

Figure 3 ***Immunohistochemistry (40x). Anti-Treponema antibody-positive technique for spirochetes with microorganisms attached to the edge of the intestinal surface (yellow).***

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In view of these findings, complete serology was performed with treponemal and non-treponemal tests as well as tests for HIV and hepatitis B and C virus, with negative results.

Given that infection by *treponema pallidum* is the most common aetiology of intestinal spirochetosis despite negative serology for Treponema, in view of the pathological anatomy and the patient's clinical findings, it was proposed to start treatment with penicillin G benzathine for 3 weeks.

However, given the epidemiological context of the patient with an absence of risk factors for infection by *treponema pallidum* and no other data suggesting a syphilitic aetiology (absence of skin or eye lesions or involvement of the central nervous system), the atypical location of the aphthae in the right colon, which in the case of syphilis they are usually found in more distal segments of the intestine or in the rectum and the negative serology for *Treponema*, which has a high specificity and sensitivity, a slow incubation stool culture is requested to screen for other species of the spirochetes genus.

The patient was reviewed one month later and showed no clinical improvement with penicillin treatment. The results of the stool culture after the slow incubation were reviewed and found to be positive for *Brachyspira*. It was decided to start oral treatment with metronidazole (500 mg every 8h) for 10 days. After two weeks, the patient presented clinical remission of the symptoms, and control colonic biopsies subsequently confirmed the absence of filamentous microorganisms adhering to the colonic epithelium.

Discussion

HIS can affect the entire colon, the appendix and even the terminal ileum. Most cases of colonisation in humans by spirochetes spp. are asymptomatic. The most common form of presentation is chronic diarrhoea, although it may also manifest with abdominal pain, alternating bowel habits, rectorrhagia or spirochetemia (mainly in immunocompromised patients). It has also been reported in association with colonic intussusception.

Although the mechanism of transmission is not fully understood, it is suggested that oro-fecal transmission is most commonly implicated, followed by sexual transmission. Recent studies have shown that colonisation of the colonic epithelial surface or mucosal layers by pathogenic *Brachyspira* species was detected in 40% of IBS patients with diarrhoea[6,7].

Diagnosis is made by identification of the microorganism on histological examination using specific techniques. The use of immunohistochemical (IHC) techniques with anti-T. pallidum antibodies is positive due to cross-reactivity with the genus *Brachyspira*. It is advisable to perform a stool culture with a slow incubation period to look for the growth of bacteria of the genus *Brachyspira*.

Other causes of diarrhoea; infectious and digestive absorption disorders, inflammatory bowel diseases and/or neoplastic diseases should be excluded before specific diagnostic techniques are requested. Differential diagnosis with *Treponema Pallidum* infection[8] should be made especially in men who have sex with men and in patients with HIV infection; by specific serology and evaluation of extraintestinal manifestations. The use of serological testing may be limited in patients with advanced immunosuppression and/or early disease.

Regarding treatment, a expectant attitude is recommended, reserving antibiotic treatment for those patients with persistent symptoms and no other demonstrable pathology. The treatments used are diverse, both in terms of dosage and duration, although metronidazole is the most commonly used. If treated, a follow-up biopsy is recommended to confirm eradication.

This case illustrates a controversial and extraordinarily rare cause of chronic diarrhoea, but should be considered in the differential diagnosis of this entity, especially in patients with predisposing risk factors.

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CLINICAL CASE

LARGE INTRATHORACIC COLLECTION SECONDARY TO ACUTE CHRONIC PANCREATITIS DISPLACING LARGE HIATAL HERNIA, AN UNCOMMON PRESENTATION.

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Abstract

The case of a 60-year-old woman with a history of chronic alcoholism and chronic liver disease is presented as a clinical case. During a hospitalization, a diagnostic imaging test reveals a possible complicated chronic pancreatitis with multiple abdominal collections. Of note is the displacement of one of the collections at the thoracic level along with a pre-existing large hiatal hernia, which, in turn, is compressed and laterally displaced by the collection, causing abdominal pain and dyspnea in the patient.

Literature on intrathoracic collections secondary to complicated chronic pancreatitis is scarce. Therefore, in a patient presenting with typical abdominal pain of pancreatitis and dyspnea, it is mandatory to consider this condition in the broad differential diagnosis that needs to be established.

Keywords: hernia, collection, pancreatitis.

Introduction

Chronic pancreatitis arises as a consequence of repeated acute inflammatory insults to the pancreas, resulting in endocrine and exocrine dysfunction requiring replacement treatment. It is associated with a wide range of symptoms1 , including diarrhoea due to maldigestion of protein-rich food because of a deficiency of the enzymes necessary for its metabolism.

However, episodes of acute chronic pancreatitis may occur, with decompensation of the already impaired baseline pancreatic function2. Clinically, such episodes manifest with abdominal girdle pain in the epigastrium, together with mild elevation of acute phase reactants and hyperlipaemia with less marked elevations than in acute pancreatitis.

Imaging usually shows an atrophic pancreas with minimal oedema and rarefaction of adjacent fat, with the possibility of peripancreatic collections and collections at the level of the splenocolonic ligament. An uncommon location of these collections is at the intrathoracic level3 , which compresses the usual anatomical structures at that level, generating a space compromise that the patient may manifest clinically with dyspnoea.

Due to the infrequency in clinical practice and in the literature of this intrathoracic presentation, we present the

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clinical case of a 60-year-old woman with chronic alcoholism and chronic liver disease, who is diagnosed with chronic pancreatitis complicated by an intrathoracic collection that displaces the known hiatal hernia and other structures, with significant clinical repercussions.

Clinical Case

A 60-year-old patient with a history of chronic alcoholism and chronic liver disease, who attended the emergency department for abdominal girdle pain in the epigastrium, radiating for 3 days, with no other associated symptoms. She mentioned that she had presented the same symptoms on other occasions, having been diagnosed with acute pancreatitis on previous admissions based on clinical and analytical criteria.

Analytically, there was an increase in acute phase reactants (CRP 50 mg/dL Leukocytes 13500 mm3 at the expense of neutrophilia (8500mm3)) as well as hyperlipidaemia (1300 mg/dL), ruling out intercurrent infectious symptoms due to organs and systems.

The patient, presenting clinical and analytical criteria for a new episode of acute pancreatitis, was admitted to the Digestive Department for evolution and monitoring.

During hospitalisation, the patient began to present dyspnoea on medium exertion that evolved to minimal exertion in a few days, together with persistent abdominal pain and oral intolerance, and it was decided to perform a thoracoabdominal CT scan to rule out complications.

A thoracoabdominal axial tomography was performed, which showed portal hypertension and splenomegaly due to known chronic liver disease, as well as findings that raised suspicion of chronic pancreatitis (presence of atrophic pancreas), in turn complicated by thrombosis of the splenic vein and multiple well-defined and encapsulated collections. These collections are distributed along the tail of the pancreas, the spleno-colonic ligament and at the retrogastric level. The herniation of the latter together with the gastric chamber towards the thorax is striking, causing a displacement of the latter superiorly and medially, data that would justify the patient's symptoms. Free intraperitoneal fluid, bilateral pleural effusion and collapse of the lower lobes were also observed (Figures 1-3).

Following tomographic findings, medical treatment was intensified, an absolute diet was maintained and parenteral nutrition was started in order to meet caloric and protein

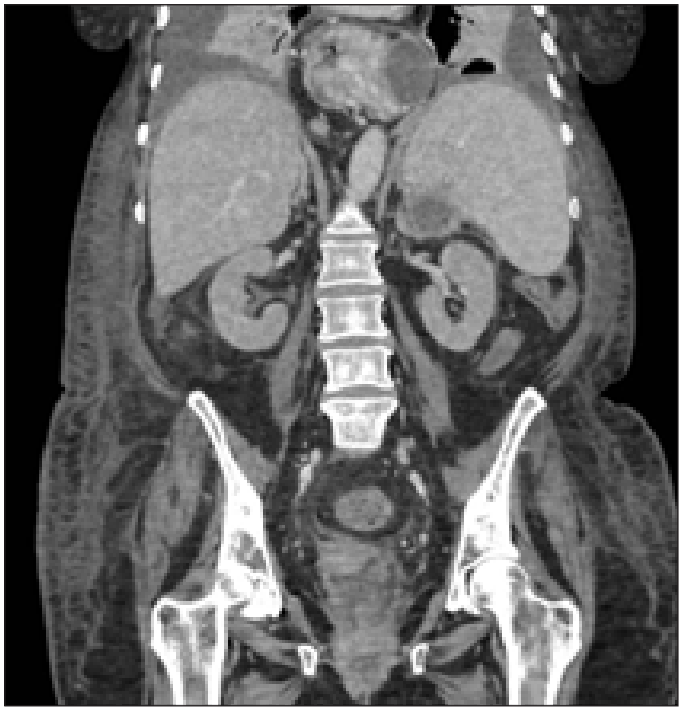

Figure 1. ***Coronal CT scan of the abdomen showing an intrathoracic collection associated with gastric chamber herniation, which is displaced superiorly and medially by the collections.***

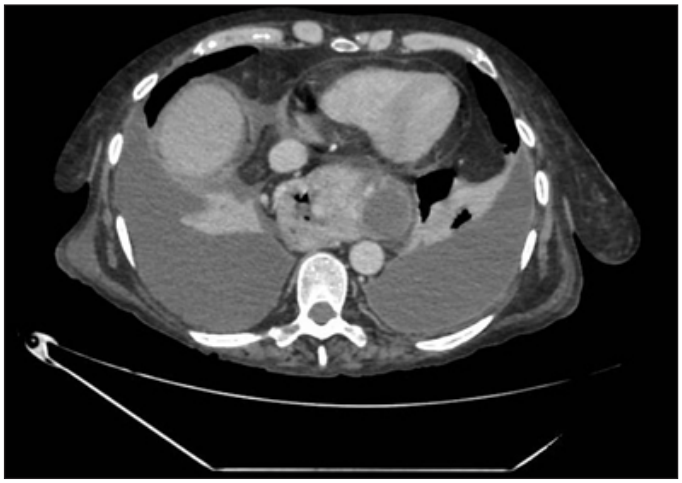

Figure 2. ***Cross-sectional abdominal CT scan showing gastric herniation together with collections secondary to acute chronic pancreatitis. In addition, bilateral pleural effusion and collapse of the lower lung lobes due to space conflict are seen.***

requirements, with close monitoring of the collections described. The clinical evolution was satisfactory, with clinical improvement, decrease in reactants and stabilisation of the collections, some of which decreased in size, especially the intrathoracic one.

Finally, on consolidation of the clinical, analytical and radiological improvement, the patient was discharged without requiring any invasive therapeutic measure, with outpatient follow-up of the collections described. Enzyme replacement

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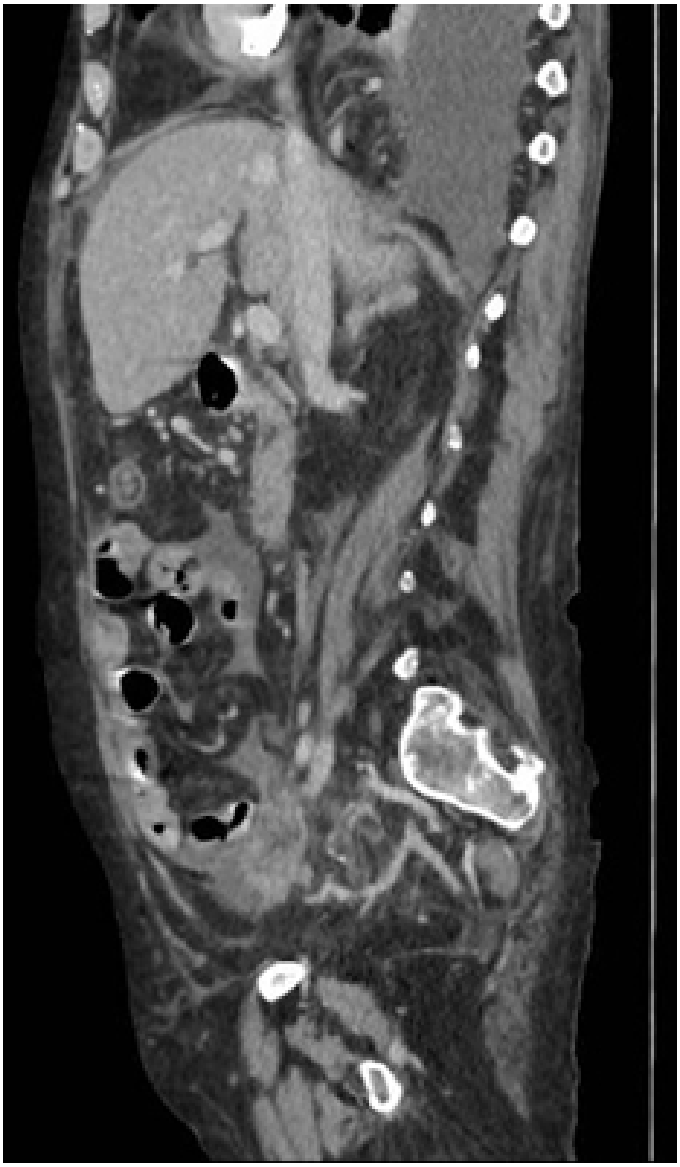

Figure 3. ***Sagittal CT scan of the abdomen showing an intrathoracic collection. Other collections are also seen at the retrogastric level, in the tail of the pancreas and in the splenocolonic ligament with no signs of complication.***

therapy was added to the usual chronic treatment for findings of chronic pancreatitis, with dosage adjustment in consultations.

Discussion

Chronic pancreatitis is an entity that should be suspected in patients presenting with repeated episodes of acute pancreatitis susceptible to hospital admission. This pathology presents clinical (abdominal pain, exocrine/endocrine insufficiency, nutritional deficits, among others), analytical (elevated acute phase reactants and hyperlipaemia, but to a lesser extent than in isolated cases of acute pancreatitis) and radiological criteria that support its diagnosis.

In this case, an atypical clinical presentation of acute chronic pancreatitis, namely intrathoracic collections, has been reported. After an exhaustive review of the literature, cases of acute pancreatitis secondary to herniation of the pancreas at the thoracic level have been found, although the literature is scarce with respect to the presence of collections at this level[1-3].

For this reason, in the case of a patient with abdominal pain typical of pancreatitis associated with dyspnoea and persistent oral intolerance, it is essential to rule out complications intrinsic to the underlying pathology, such as intrathoracic collections, as part of the broad differential diagnosis that must be established. The complication observed in this case, given the infrequency of its manifestation, represents a diagnostic challenge that must be taken into account in daily clinical practice.

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PERFORATION OF A PEPTIC ULCER WITH MIGRATION OF HEMOSTATIC CLIP: A RARE COMPLICATION IN THE TREATMENT OF UPPER GASTROINTESTINAL HAEMORRHAGE.

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Abstract

Hemostatic clips are one of the most common treatment options for upper gastrointestinal haemorrhage, allowing for monotherapy in Forrest IIa or higher-grade bleeding. Complications associated with them are infrequent, limited to erosions and minor bleeding related to their deployment. We present the case of a patient with upper gastrointestinal haemorrhage secondary to a duodenal peptic ulcer. The patient was treated using a combination of various hemostatic methods, which resulted in perforation of the ulcer and migration of a hemostatic clip into the duodeno-pancreatic groove.

Keywords: hemostatic clip, perforation, upper gastrointestinal haemorrhage.

Introduction

Upper gastrointestinal haemorrhage (UGH) is one of the most frequent digestive pathologies, especially secondary to peptic ulcer. About 30% require endoscopic treatment[1]. The most common are the use of adrenaline for sclerotherapy and mechanical therapy using haemoclips. Serious complications secondary to the use of these methods are rare. Adrenaline may cause tachycardia and hypertension due to its passage into the peripheral blood. Regarding haemostatic clips, with an efficacy of more than 90% in achieving cessation of bleeding, complications are rare, with erosions secondary to their use and intestinal perforation after their release having been described[2]. However, we present the case of a patient with UGH who presented migration of a haemoclip into the duodenopancreatic groove through the perforation of a peptic ulcer, a complication that has not been described to date.

Clinical Case

We present a 69-year-old patient with haematochezia and haemodynamic instability suggestive of rapid transit in the context of an upper gastrointestinal haemorrhage. Laboratory tests showed a decrease of 5 haemoglobin points. An urgent upper gastrointestinal endoscopy was performed and a 23mm ulcer was found in the first superior duodenal flexure, with active drooling bleeding and visible vessel (Forrest IB), which was treated with adrenaline injection, placement of haemoclips, haemostatic clamp and haemospray to control the haemorrhage.

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After 48 hours, the patient began to show signs of gastrointestinal haemorrhage, abdominal pain and haemodynamic instability. An angio-CT scan was requested, which showed perforation of the previously described ulcer and an image of a foreign body in the duodeno-pancreatic groove of about 9 mm, compatible with a migrated haemostatic clip.

After spontaneous cessation of bleeding, the patient remained asymptomatic, allowing conservative management of the perforation, and was finally discharged.

Discussion

Haemostatic clips are a fundamental pillar in the management of UGH and can be used in monotherapy in Forrest IIa and IIb haemorrhages. They are a safe treatment with few complications, although duodenal perforation following their use has been described, but very infrequently. The particularity of this case is the migration of the clip into the duodenopancreatic groove, a complication that has not been described. Management of the perforation will depend on the patient's condition; in case of instability or peritonitis, it will be surgical[3]. In cases where there is no such evidence, conservative initial treatment with close monitoring of the patient may be consid.

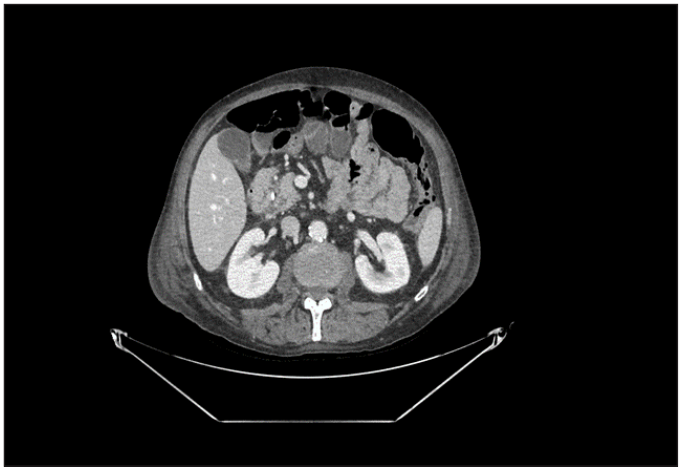

Figure 1. ***In this image we can see the contained perforation and a hyperdense image corresponding to the migrated clip in the duodeno-pancreatic groove.***

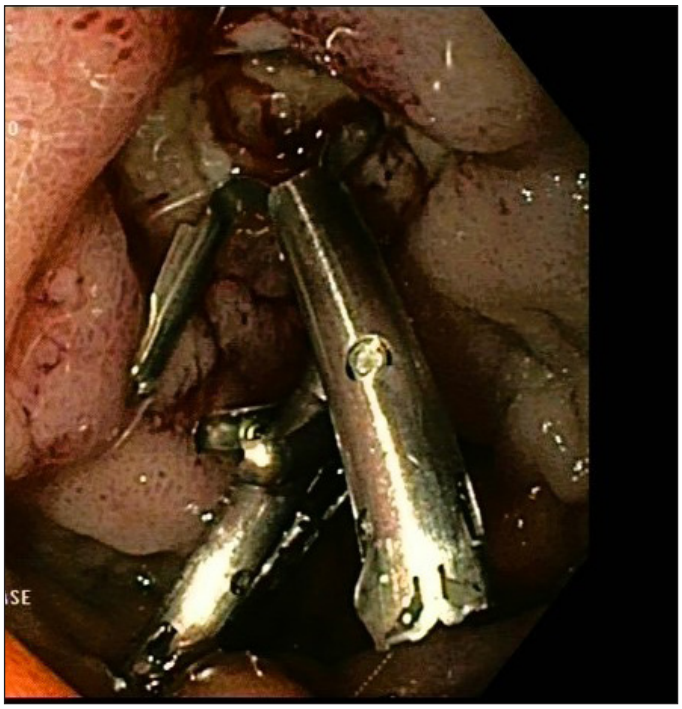

Figure 2. ***Figure corresponding to the upper gastrointestinal endoscopy in which we can see the ulcer after treatment with several clips.***

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GREEN APPLE AND RED CONGO: ATYPICAL DYSPHAGIA COLOURS.

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Abstract

Amyloidosis is a rare disease that consists of the extracellular deposition of insoluble protein subunits known as fibrils, resistant to proteolytic degradation. It can occur in any organ of the body, causing its slow and gradual failure.

Specific involvement of the gastrointestinal tract interferes with its structure and function, most commonly in the liver and small intestine, with esophageal involvement being a rare entity, and whose main clinical manifestation is reflux. On the other hand, presentation in the form of dysphagia is highly uncommon.

Keywords: esophageal amyloidosis, dysphagia, congo red.

Clinical Case

71-year-old male, hypertensive and dyslipidaemic. At the age of 40, he was referred to the otorhinolaryngology department for his debut with dyspnoea, and was diagnosed with laryngeal amyloidosis. At 70 years of age, he began with progressive dysphagia to solids and liquids, denying pyrosis, weight loss, abdominal discomfort or other symptoms, with unremarkable blood tests. Esophagogastroduodenoscopy was performed, showing granular esophageal mucosa (Figure 1), from which biopsies were taken. Barium swallow was also performed, which showed no evidence of swallowing disorder. The biopsies showed submucosal deposits of amorphous eosinophils, positive for Congo red staining (Figure 2), and serum amyloid P, with green birefringence by polarised light microscopy (Figure 3), these findings being compatible with the diagnosis of esophageal amyloidosis.

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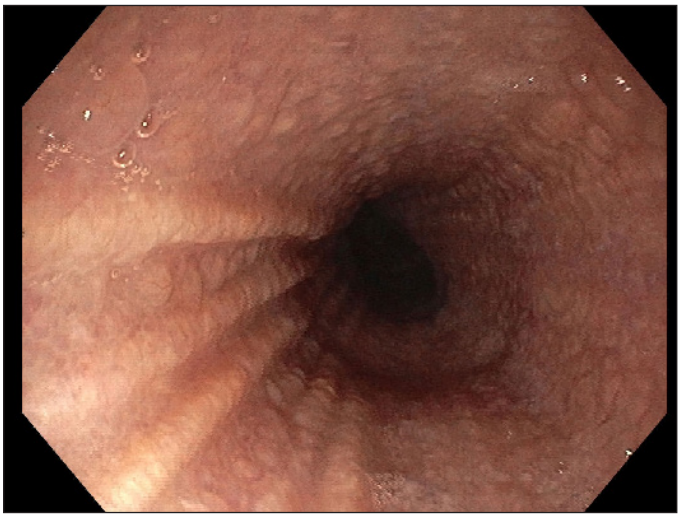

Figure 1. ***Endoscopic view of the proximal oesophagus, showing granular esophageal mucosa.***

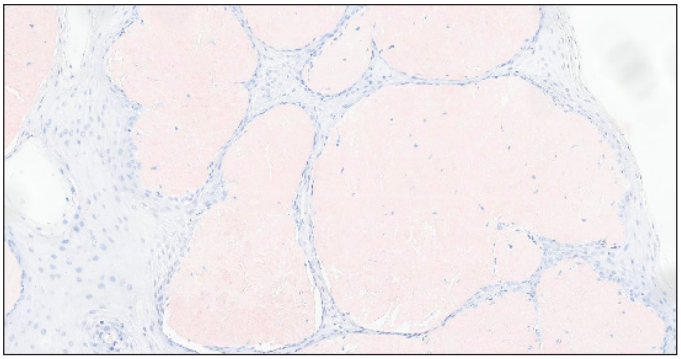

Figure 2. ***Visualisation of amyloid deposits by Congo Red staining.***

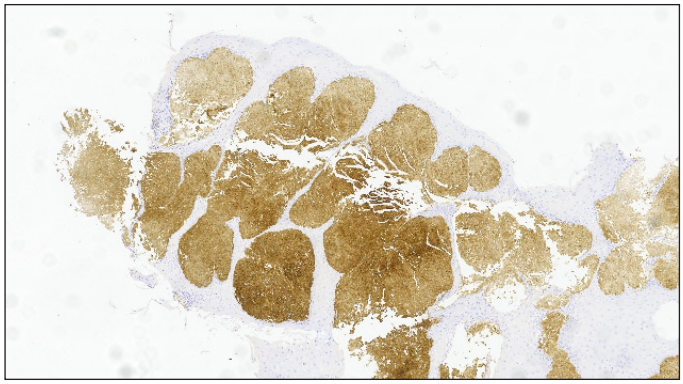

Figure 3. ***Applying polarised light to the tissue section shows apple-green birefringence.***

Discussion

Esophageal amyloidosis is usually silent and, if symptomatic, gastro-esophageal reflux is the most common clinical manifestation. Dysphagia, on the other hand, is a rare entity in this context. Endoscopically, mucosal friability, erosions, ulcers and submucosal haematomas are usually observed. Given the variability of endoscopic findings, as well as the presentation of non-specific symptoms, confirmatory diagnosis requires histopathological studies such as Congo red staining or birefringence under polarised light.

The mechanism of dysphagia secondary to esophageal amyloidosis is unknown, although part of it is attributed to a certain component of dysmotility secondary to atrophy due to nerve damage and pressure generated by the amyloid deposit as it settles between the muscle fibres. For this reason, the use of functional tests such as barium transit or esophageal manometry are also of interest, as they can offer characteristic radiological patterns in some cases (esophageal dilatation with distal narrowing)[1,2].

To date, there are hardly any described cases of dysphagia as the main manifestation of this disease, so examples such as this one should help us not to forget this diagnostic possibility, integrating esophageal amyloidosis into the differential diagnoses of dysphagia.

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