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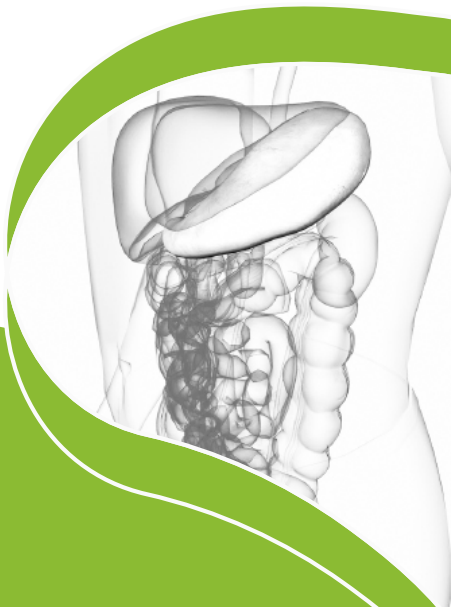
ANDALUSIAN JOURNAL OF DIGESTIVE PATHOLOGY



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.

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- 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.

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ORIGINAL

PROFILE OF PATIENTS DIAGNOSED WITH HYDROGEN-PRODUCING INTESTINAL BACTERIAL OVERGROWTH AND INTESTINAL METHANOGENIC OVERGROWTH IN A SECOND LEVEL HOSPITAL

Saldaña García L, Hernández Pérez AM, Méndez Sánchez IM, López Vega MC, Fernández Moreno N, Pérez Aisa A
COSTA DEL SOL HOSPITAL. MALAGA.

Abstract

Introduction and objectives: intestinal methanogenic overgrowth (IMO) is a recognized entity that has recently been included within the profile of intestinal bacterial overgrowth (SIBO). This study is carried out with the objective of describing the clinical-epidemiological characteristics of patients with bacterial overgrowth in hydrogen (SIBO-H) and IMO and analyzing the differences between groups in terms of the variables studied.

Material and methods: observational, retrospective, single-center study. Patients seen in the Digestive Department were included, in whom a breath test with oral glucose load had been performed to evaluate SIBO-H and IMO. The clinical-epidemiological characteristics of the patients were analyzed and a comparative analysis was carried out between SIBO-H and IMO.

Results: 116 patients with symptoms suggestive of SIBO were analyzed, of which 26 were eligible with a positive result for hydrogen or methane (22.41%). SIBO-H was diagnosed in 50% (13) and IMO in 50% (13). The predominant symptoms in both groups were abdominal pain, bloating and diarrhea. The risk factors identified were surgical resections with anastomosis, diabetes mellitus and hypothyroidism. No differences were

Leticia Saldaña García
Costa del Sol Hospital. Malaga.
letisg93@gmail.com

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found between both groups in terms of clinical-epidemiological characteristics and treatment.

Conclusions: no significant differences were found regarding the variables studied in a probable relationship with a small sample. It is necessary to continue studying the characteristics of both groups in order to implement effective diagnosis and treatment strategies for an entity of growing interest in Digestive System consultations.

Keywords: SIBO, SIBO-H, IMO, treatment.

Abbreviations

SIBO: intestinal bacterial overgrowth.

SIBO-H: intestinal hydrogen-producing bacterial overgrowth.

IMO: intestinal methanogenic overgrowth.

OGTT: oral glucose overload breath test.

IBD: inflammatory bowel disease.

DM: diabetes mellitus.

IBS: irritable bowel syndrome.

PPIs: proton pump inhibitors.

FODMAPS: fermentable oligosaccharides, disaccharides, monosaccharides and polyols.

Introduction

The normal small intestine, has lower levels of microbial colonisation compared to the colon, when this balance is significantly disturbed it gives rise to the SIBO. This is characterised by the presence of excessive numbers of bacteria in the small intestine leading to pathological fermentation of nutrients and maldigestion of substrates that are normally fully absorbed in the small intestine, leading to symptoms resulting from excess gas production[1].

Quantitative culture of the proximal small bowel aspirate is the gold standard for objectively measuring the number of bacteria in the small intestine, with a bacterial colony count of ≥10^3 colony-forming units per millilitre (CFU/mL) in a duodenal/jejunal aspirate recently established as diagnostic of SIBO[2]. However, in order to be performed, the implementation of an upper endoscopy is necessary with the consequent risks of this invasive test. Therefore, a widely accepted, easy and inexpensive alternative method for the diagnosis of SIBO, based on the premise that human cells are incapable of producing hydrogen or methane, is the measurement of these gases in the breath after ingestion of a carbohydrate substrate such as glucose or lactulose[3].

The human microbiome is strongly intertwined with health and disease. In addition to bacteria, viruses and eukaryotes, numerous archaea are found in the human gastrointestinal tract and are responsible for methane production[4]. Recently, with the recognition of their role in the pathophysiology of SIBO, a new concept has been introduced, namely methanogenic intestinal overgrowth (MOI). Despite this, many aspects such as the clinical profile, the sensitivity of diagnostic tests and medical treatment, which to date has been largely empirical, remain an enigma.

In 2020, *The American Journal of Gastroenterologist* (AJG) published a clinical guideline on SIBO in an attempt to re-evaluate the evidence to date and propose recommendations to characterise and standardise the management of these patients in routine clinical practice[5]. The AJG concludes that most of the recommendations are weak and the evidence is of low quality and emphasises the current unmet needs in SIBO research, as well as the controversies in the field regarding the clinical profile, diagnosis and treatment of these patients.

In our centre, oral glucose overload breath test (OGTT) has been routinely performed to measure hydrogen concentrations in exhaled air to diagnose hydrogen-producing bacterial overgrowth (SIBO-H) in patients with suggestive symptomatology and predisposing factors[6]. Given that up to 38% of the general population is methane fermenting[7], measurement of methane concentrations has recently been incorporated into the assessment of IMO with the aim of improving the diagnostic spectrum of this entity.

These recent changes in the diagnostic approach to this entity have motivated this study to describe the clinical-epidemiological characteristics of patients with SIBO-H and IMO and to analyse the differences between the two groups.

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Material and methods

An observational, retrospective and single-centre, retrospective study was conducted where adult patients seen in the Digestive System consultations of the Costa del Sol University Hospital were included, from november 2022 to june 2023, who presented symptoms suggestive of SIBO, in whom OGTT (75 g of glucose in 200 mL of water) had been performed measuring hydrogen and methane concentrations in exhaled air to assess SIBO-H and IMO according to standard clinical practice.

The selected patients had a symptom profile suggestive of SIBO such as abdominal pain, bloating, gas, distension, flatulence, constipation or diarrhoea, as well as risk factors for SIBO such as anatomical bowel or motor complex disorders.

Patients were given recommendations to follow in the 48 hours prior to the test. These included a minimum fasting period of 12 hours, not smoking from the night before, avoiding fermentable carbohydrates and dietary fibres for at least 24 hours beforehand. They were also advised not to exercise beforehand and to brush their teeth in the morning with antiseptic solution. The test was performed at least four weeks after taking antibiotics and two weeks after colon cleansing for endoscopic or surgical procedures.

Initially, a basal alveolar sample was taken which had to be less than 10 ppm hydrogen. Values between 10 and 20 ppm pointed to incomplete fasting before the test or slow digesting food intake the day before the test, so they were recalled for a repeat test after specific re-education.

For the breath test, 75 gr of glucose diluted in 200 mL of water was used as substrate, using a diagnostic kit with sample collection tubes supplied by ISOMED PHARMA for breath measurement and sampling. The basal sample was collected and after dilution, alveolar samples were taken with forced expiration at 15-minute intervals for 120 minutes. Symptoms during the test were recorded. Attention was paid to breath sampling, storage and stability of the sample and to the specific instructions of the manufacturer, in order to ensure the accuracy of the test.

The results were submitted for combined hydrogen and methane reading with QuinTron at the ISOMED PHARMA reference laboratory.

The test was considered negative when no pathological increase in hydrogen or methane concentrations in exhaled air above baseline was identified during 120 minutes. An increase in exhaled air hydrogen concentration of 20 ppm above baseline at 90 minutes of testing was considered to be compatible with SIBO-H. An increase of 10 ppm above baseline in exhaled air methane concentration at any time during the test (120 minutes) was considered compatible with IMO.

The primary outcome variable was SIBO phenotype (SIBO-H or IMO). Covariates were age, sex, presence of symptoms leading to the test and symptoms during the test, predisposing factors, medical treatment used, subsequent follow-up and the performance of a second OGTT to assess the decrease in hydrogen or methane production after treatment. A comparison of both groups was made between the variables studied.

Student's t-test was used for quantitative variables and Chi-Square for qualitative variables. A value of $p<0.05$ was considered statistically significant.

Results

We analysed 116 patients with symptomatology suggestive of intestinal bacterial overgrowth in whom OGTT had been performed to evaluate SIBO-H and IMO, of whom 26 were eligible with positive hydrogen or methane result (22.41%). SIBO-H was diagnosed in 50% (13) and IMO in 50% (13) (Table 1), with a median age of 53 and 57 years respectively (Table 2).

Associated risk factors were: hypothyroidism 15.4% (2) in both groups, bowel resection with anastomosis 23.1% (3) in both groups and in the case of SIBO-H, diabetes mellitus 23.1% (3). All patients older than 65 years[3] tested positive for IMO. One patient with IMO (7.7%) had irritable bowel syndrome (IBS) (Table 2).

The most frequent symptom was diarrhoea 53.8% (7) in both groups. Abdominal pain was more frequent in patients with SIBO-H 46.1% (6) versus 38.5% (5) in the IMO group. For meteorism, it was more frequent in IMO patients 53.8% (7) versus 38.5% (5) in SIBO-H patients (Figure 1). No cases of constipation were identified in the studied sample. There were no statistically significant differences between the two groups for the variables studied.

Of the 26 patients who tested positive, 17 (9 with SIBO-H and 8 with IMO) received medical treatment. The most commonly used treatment for SIBO-H was Rifaximin 88.9% (8). In IMO Rifaximin and Metronidazole 50% (4) and Rifaximin and

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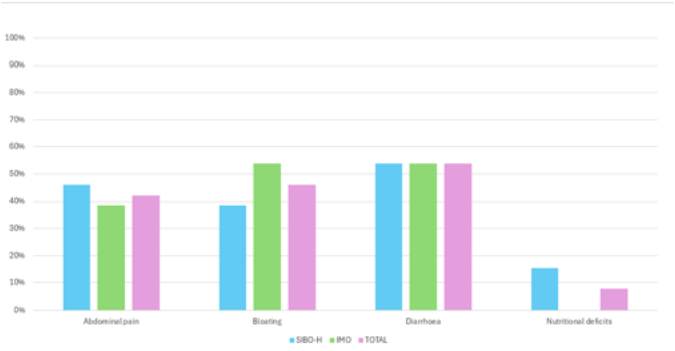

Figure 1. ***Symptomatology associated with hydrogen-producing intestinal bacterial overgrowth and methanogenic intestinal overgrowth.***

Neomycin 37.5% (3) were used. The test was repeated with the intention to assess treatment outcome in one patient with SIBO-H and in three with IMO. The post-treatment test was negative in only one patient with IMO.

Discussion

SIBO is defined by the presence of an abnormal amount of bacteria in the small intestine, which ferment carbohydrates and produce gas leading to the occurrence of symptoms such as bloating, abdominal pain, diarrhoea and constipation.

Although most patients with SIBO produce hydrogen, 30-38% are colonised with archaeal species. Archaea are anaerobic organisms that produce methane and are resistant to many systemic antibiotics. The excessive presence of archaea in the small intestine, and the symptoms resulting from nutrient fermentation, is known as IMO; a newly recognised entity within the SIBO profile. However, it is unclear whether IMO is distinguished by a distinctive set of gastrointestinal symptoms and predisposing conditions[7].

Culture of jejunal aspirate obtained by upper gastrointestinal endoscopy is the gold standard for the diagnosis of SIBO, with a bacterial colony count of ≥10^3 CFU/mL being considered diagnostic[8]. Breath tests are performed in daily clinical practice for the diagnosis of many common conditions of the gastrointestinal tract such as carbohydrate maldigestion, oro-cecal transit dysfunction or disturbances and SIBO. Substrates such as glucose, lactulose, fructose, sorbitol, sucrose and inulin can be used. The rationale of the breath test is that both hydrogen and methane are produced exclusively through microbial fermentation in the gut. Intestinal microorganisms readily digest carbohydrates, resulting in the production of these gases, which then diffuse into the abdominal venous circulation and are transported to the lungs, where they can be detected in the exhaled breath[3]. Quantitative measurement of hydrogen and methane in exhaled air after ingestion of a quantity of carbohydrates is an indirect method and a non-invasive, easy and readily available test recommended by scientific evidence to assess SIBO as an alternative to jejunal aspirate[5]. The sensitivity of the lactulose oral overload breath test has ranged from 31% to 68% and the specificity has ranged from 44% to 100%, while the sensitivity of glucose oral overload breath tests has ranged from 20% to 93% and the specificity from 30% to 86% compared to small bowel aspirate cultures[5]. The lactulose-overloaded breath test results in a higher number of false positives, which is why glucose is considered the substrate of choice to administer as performed in our study[1].

In the evidence reviewed, the prevalence of SIBO is around 30%[7] vs. 22.41% in our study. Regarding IMO, a prevalence of up to 38.8% has been reported in patients with SIBO[7] vs. 50% in our study. In accordance with the literature, we found a predominance of SIBO in the female sex (69.2%) and the mean age was 53 years, similar to that described in other studies[7]. It is striking that all patients in the sample older than 65 years were

	SIBO-H	IMO	Total
Breath test result	Positive for hydrogen	Positive for methane	
	13 (50%)	13 (50%)	26 (100%)
Symptoms during the test			
	5 (38.5%)	1 (7.69%)	6 (23.1%)
SIBO: hydrogen-producing intestinal bacterial overgrowth; IMO: intestinal methanogenic overgrowth			

Table 1. ***Results of the oral glucose overload breath test to assess intestinal hydrogen-producing bacterial overgrowth and intestinal methanogenic overgrowth.***

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	SIBO-H	IMO	Total
Sex			
Male	5 (38.5%)	3 (23.1%)	8 (30.8%)
Female	8 (61.5%)	10 (76.9%)	18 (69.2%)
Age			
Median (IQR)	53 (32.5%)	57 (16.5%)	53 (15.8%)
Risk factors			
Smoker	1 (7.7%)	0	1 (3.8%)
Anatomical disorders			
Surgical resections with anastomosis	3 (23.1%)	3 (23.1%)	6 (23.1%)
Small bowel diverticulum	0	0	0
Stenosis	0	0	0
Gastric bypass	0	0	0
IBD with fistula	0	0	0
Motor complex disorders			
DM	3 (25%)	0	3 (11.5%)
IBS	0	1 (7.7%)	1 (3.8%)
Radiation enteritis	1 (7.7%)	0	1 (3,8%)
Hypothyroidism	2(15.4%)	2 (15.4%)	4 (15.4%)
Scleroderma	0	0	0
Parkinson	0	0	0
Opioids	0	0	0
Coeliac disease	0	0	0
Others			
Use of PPIs	1 (7.7%)	2 (15.4%)	3 (11.5%)
Older than 65 years old	0	3 (23.1%)	3 (11.5%)
Obesity	1 (7.7%)	0	1 (3.9%)
Carbohydrate test suggested SIBO-H or IMO			
	3 (25%)	4 (30.76%)	7 (26.9%)

SIBO: hydrogen-producing intestinal bacterial overgrowth; IMO: methanogenic intestinal overgrowth; IBD: Inflammatory Bowel Disease; IBS: Irritable Bowel Syndrome; PPIs: proton pump inhibitors;

Table 2. ***Epidemiological factors associated with intestinal hydrogen-producing intestinal bacterial overgrowth and intestinal methanogenic overgrowth.***

diagnosed with IMO, which supports the positive relationship between age and colonisation by methanogenic archaea[7].

Regarding predisposing factors, although IBS is one of the conditions most commonly assessed as being linked to SIBO[5,9], in this study it was present in only 7.7% of patients with IMO. Mechanical anatomical disorders of the small bowel[6] and motility disorders have been linked to abnormal accumulation of bacteria in the small bowel[10], both of which were present in the patients under study with a predominance of intestinal resections with anastomosis and hypothyroidism in both SIBO-H and IMO patients. Several studies suggest that 50% of patients with thyroid dysfunction have SIBO[11]. Diabetes mellitus has been shown to be significantly more prevalent in patients with SIBO (12)[7], however, in our study it was present in only 25% of patients with IMO and in no SIBO-H patients.

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	SIBO-H (n=9)	IMO (n=8)	Total (n=17)
Treated Predisposing Factor			
	2 (15.38%)	3 (23.1%)	5 (19.2%)
Medical treatment used			
Neomycin and Rifaximin	0	3 (37.5%)	3 (17.6%)
Rifaximin and Metronidazole	1 (11.1%)	4 (50%)	5 (29.4%)
Rifaximin	8 (88.9%)	1 (12.5%)	9 (52.9%)
SIBO control after treatment			
Time since end of treatment			
Mean (days)	66	128	103
Repeat breath test after treatment			
	1 (11.1%)	3 (37.5%)	4 (15.38%)
Negative test result			
	0	1 (12.5%)	1 (3.84%)
SIBO: hydrogen-producing intestinal bacterial overgrowth; IMO: intestinal methanogenic overgrowth;			

Table 3. ***Treatment used in patients diagnosed with intestinal hydrogen-producing bacterial overgrowth and intestinal methanogenic overgrowth.***

It has been postulated that treatment with PPIs, with the consequent decrease in gastric acidity, could be a risk factor for the development of SIBO[13]; however, the scientific evidence in this regard is contradictory[5]. In our study, 7.7% of patients with SIBO-H and 15.4% of patients with IMO were treated with PPIs, which is to be expected given the high consumption of PPIs in the general population.

In terms of symptomatology, abdominal pain with bloating, diarrhoea and meteorism are the most commonly described symptoms in the scientific evidence[5]. Diarrhoea has been most commonly associated with SIBO-H[14], however, in our study no differences in symptomatology were found between patients with SIBO-H and IMO.

Multiple studies have shown that methane-positive OGTT is related to constipation and that the level of methane in exhaled air is proportional to the degree of constipation[14,15]. However, none of the patients diagnosed with OMI in this study had constipation.

Evidence suggests antibiotic treatment in patients with SIBO to eradicate the overgrowth of microorganisms in the small intestine[5]. In the case of SIBO-H, Rifaximin, although lacking in high quality studies, is supported by the most evidence[16] and has been the most commonly used monotherapy in the patients with SIBO-H under study. In the case of patients with IMO, evidence suggests that the combination of Rifaximin and Neomycin is able to reduce methane to undetectable levels[17]. In our study, 37.5% of patients with IMO received Rifaximin and Neomycin in combination.

There are other non-drug treatments used in patients with SIBO with little evidence such as the use of probiotics[18], low FODMAPS (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diet[19] and herbal products[20] which were not used in the patients under study.

The limitations of our study include its retrospective design, which prevents us from determining causality, as this requires prospective longitudinal studies. Secondly, the small sample size may have influenced the absence of significant results. On the other hand, not all patients diagnosed and treated had been re-evaluated at the time of this study, largely due to the time lag, which prevented us from assessing symptomatic improvement after treatment or breath test negativities.

As strengths, our study analyses the characteristics of patients with IMO; an entity little studied to date and with many enigmas in terms of clinical profile, diagnosis and management.

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Conclusions

In view of the results obtained in the present study SIBO is a relatively frequent entity in our study (22.41%). The routine implementation of measurement of hydrogen and methane concentrations in exhaled air has allowed the diagnosis of IMO in 50% of patients with SIBO; however, no significant differences have been found to demonstrate distinctive features of SIBO-H and IMO in terms of epidemiological factors, symptomatology, diagnosis or treatment.

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CLINICAL CASE

EARLY STENOSIS AND DEHISCENCE OF SURGICAL ESOPHAGO-JEJUNAL ANASTOMOSIS TREATED WITH DIFFERENT ENDOSCOPIC TECHNIQUES

González Parra AC, Fernández Mascuñano M, Muñoz García-Borruel M, Rodríguez-Téllez M
VIRGEN MACARENA UNIVERSITY HOSPITAL. SEVILLE.

Abstract

Benign esophageal stenosis is a common pathology in daily clinical practice. Most cases are simple and are successfully treated with endoscopic dilation (ED) using bougies or balloons. In recurrent or refractory stenosis cases, other endoscopic options should be considered, with incisional therapy (IT) being deemed an effective and safe alternative.

We report a case of a patient with chronic gastritis, extensive multifocal intestinal metaplasia, and high-grade dysplasia in the antrum and body without visible lesions. The patient underwent total gastrectomy with Roux-en-Y reconstruction and subsequently developed early stenosis of the anastomosis, necessitating dilation with bougies, stent placement, and incisional therapy.

Keywords: anastomotic stenosis, dilation, incisional therapy.

Introduction

There are a number of well-described gastrointestinal complications following Roux-en-Y gastrectomy. One of these is stricture of the anastomosis, described in 5-46% of cases of oesophagogastric surgery[1].

Most oesophageal strictures are simple and are associated with good response to endoscopic therapy with dilatation. However, up to 10-30% of strictures may become complex, leading to increased refractoriness and the need for repeated therapies. In cases where conventional endoscopic dilatation is not sufficient, IT is positioned as a considerable alternative for refractory benign strictures[1,2,4].

However, such techniques are not without risk, with perforation being the most frequent complication (0.1-0.6% with ED and about 5.6% with IT), which is usually resolved endoscopically with prosthesis placement [2,3].

María Fernández Mascuñano
Virgen Macarena University Hospital. Seville.
mariaviso96@gmail.com

González Parra AC, Fernández Mascuñano M, Muñoz García-Borruel M, Rodríguez-Téllez M. Early stenosis and dehiscence of surgical esophago-jejunal anastomosis treated with different endoscopic techniques. RAPD 2024;47(4):152-154. DOI: 10.37352/2024474.2

Clinical case

A 66-year-old woman with no personal or family history of interest. She consulted for dyspepsia, and an upper endoscopy (EGD) was requested, which revealed chronic gastritis with extensive multifocal metaplasia and high-grade dysplasia in the antrum and body with no visible lesions (Figure 1). The case was discussed in a multidisciplinary committee and a decision was made to perform a laparoscopic total gastrectomy with Roux-en-Y reconstruction, which was performed without early complications. Two months later, the patient developed almost complete dysphagia, so a new EGD was performed, and punctiform stenosis of the anastomosis was observed (Figure 2). It was decided to dilate the anastomosis with 8 to 12 mm Savary-Gilliard bougies (Figure 3), resulting in immediate dehiscence of the anastomosis, which required the placement of a coated metal prosthesis (Ultraflex™ 120 x 23 mm) (Figures 4 & 5). Subsequent evolution was satisfactory, and the prosthesis could be removed after one month.

Six months after the procedure, the patient again reported dysphagia, and EGD was performed and identified recurrence of the stricture, which was treated with IT following the standard technique, using the IT nano scalpel and adding intralesional triamcinolone. The procedure was performed without immediate complications and the patient was discharged after 24 hours and remained asymptomatic after three months.

Discussion

Early stricture of the oesophago-jejunal anastomosis is a known complication after surgery. Endoscopic therapy is the treatment of choice for benign strictures when symptomatic, with balloon or bougie dilatation, incisional therapy or prosthesis placement being the most common options.

The ED technique is carried out by means of bougies or balloon. The first technique is based on dilatation by application of combined radial and longitudinal force, which can be performed under fluoroscopic control. The balloon, on the other hand, applies only radial force, and has the advantage of allowing direct endoscopic visualisation[1,2].

A systematic review published in 2018 concluded that both techniques are equivalent in terms of effectiveness and safety, with no differences in clinical outcomes, recurrence at twelve months, bleeding and perforation rate. Therefore, the choice of one technique or the other should be based on the

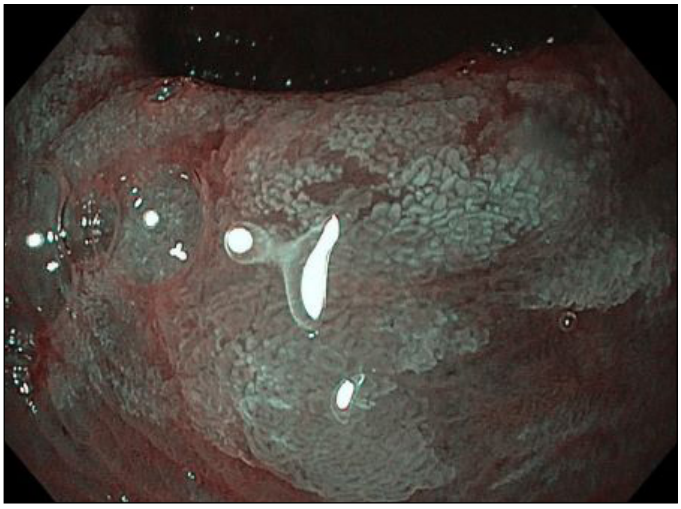

Figure 1. NBI endoscopic image of the areas of intestinal metaplasia in the gastric body.

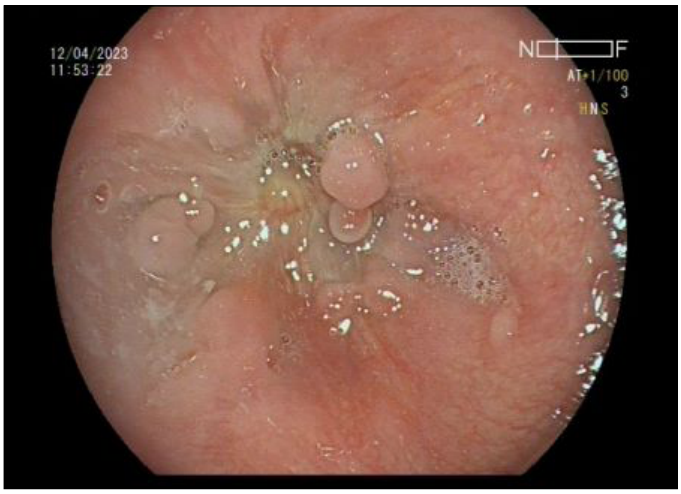

Figure 2. Endoscopic view of punctiform stricture of the oesophago-jejunal anastomosis.

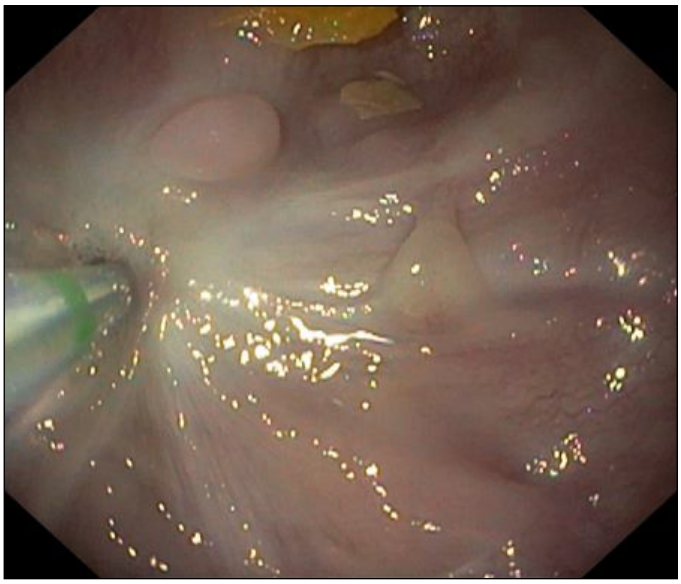

Figure 3. Endoscopic view of the stenosis, showing the canulotome through where the guides where bougies will pass through are introduced.

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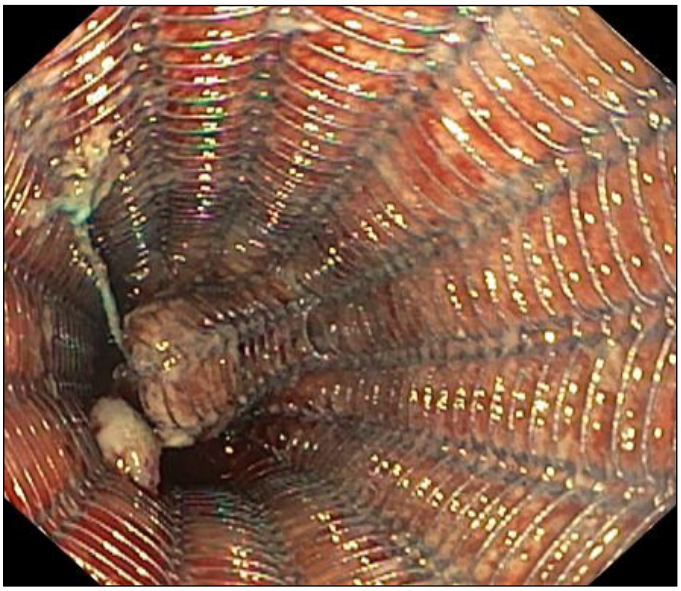

Figure 4. Endoscopic view of the coated metal prosthesis (Ultraflex™ 120 x 23 mm).

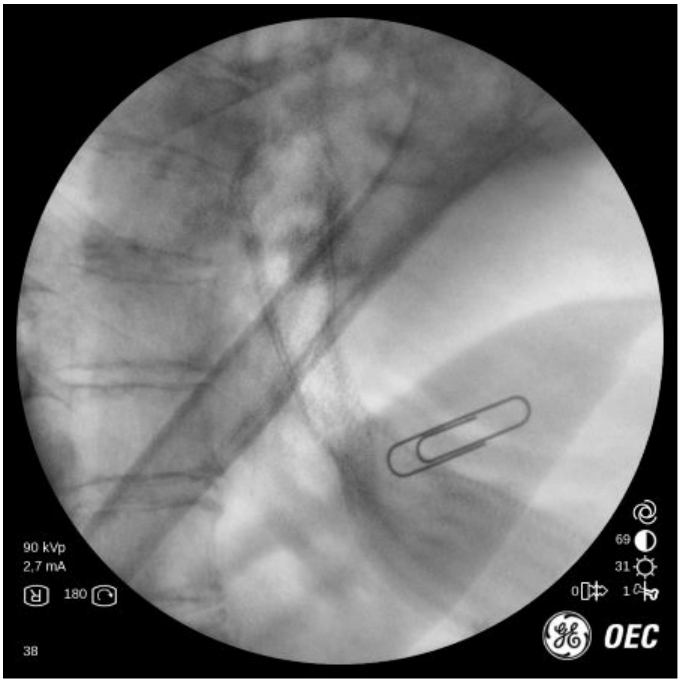

Figure 5. Normopositioned prosthesis, radiological vision.

experience of the endoscopist and the availability at each centre[3].

The goal of IT is resection of the fibrotic ring. Typical strictures to be treated with this technique are those that are benign, short (1-2 cm) and formed by fibrocycatricial tissue. There are two modalities, the radial incision and the circumferential incision, in which the fibrotic area is resected circumferentially following the axial axis of the oesophagus. The most frequent adverse effects (AE) are pain, bleeding and perforation, with the rate of AE being very low and similar to those of ED[1].

There is a randomised clinical trial comparing 62 patients with anastomotic stenosis, those treated with bougies and those treated with IT. There is no significant difference in both groups in either clinical success or AE rate[5]. However, Muto *et al.* published a retrospective cohort study comparing the efficacy of IT with ED in 54 patients with surgical oesophago-gastric stricture, concluding that there was superiority in oesophageal patency at 6 and 12 months in IT treatment over ED (65.3% vs 19.8%, p<0.005; 61.5% vs 19.8%, p<0.005)[6]. Therefore, the choice of ED or IT is controversial, prospective studies with larger sample numbers and longer term are required to draw conclusions. It seems reasonable to conclude that IT is an alternative to ED when performed by trained personnel and in short anastomotic strictures[2].

Regarding corticosteroid injection, while pre-procedure administration has not shown benefit, the addition of intralesional triamcinolone following dilatation of a post-surgical stricture statistically significantly reduces the number of procedures required to resolve the stricture, with clinical improvement of symptoms[7,8].

On the other hand, the *European Society of Gastrointestinal Endoscopy* (ESGE) is against their first-line use in benign strictures due to the potential increase in AEs, such as migration or epithelial hyperplasia that makes their removal difficult, relegating their indication to the failure of previous treatments. Prostheses are indicated as first-line palliative treatment for malignant strictures or for the resolution of leaks or perforations[3,9].

We can conclude that in some cases strictures of oesophago-gastric surgical anastomoses are challenging to manage due to their refractoriness. In these cases, endoscopic balloon or bougie dilatation and incisional therapy are effective and safe options if performed by trained staff. However, it is not a risk-free process, with perforation being the most frequent and serious complication, which is also usually resolved with endoscopic treatment, as in our case.

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CLINICAL CASE

OLMESARTAN AS AN UNCOMMON CAUSE OF ENTEROPATHY

Mendoza Rodríguez R, Fernández Cano MC, Carrero Castaño A, Redondo Cerezo E

VIRGEN DE LAS NIEVES HOSPITAL. GRANADA.

Abstract

Diarrhoea is the cardinal symptom of multiple pathologies in the digestive system, with multiple aetiopathogenesis. Chronic causes include pathologies such as coeliac disease, the main cause of villous atrophy in the small intestine. However, diarrhoea can also appear as an adverse reaction to drugs, sometimes with a pathophysiological basis in non-celiac enteropathy, causing malabsorptive syndromes. Angiotensin II receptor antagonist antihypertensives, such as Olmesartan, used to treat hypertension, diabetic nephropathy and heart failure, can cause enteropathy. Although rare, this condition should be considered in patients with severe diarrhoea and weight loss. The exact pathophysiology is unknown, but a type I immune response and inhibition of TGF-β, a key molecule in intestinal homeostasis, are suspected.

Olmesartan enteropathy occurs in both sexes, mainly in the elderly, and is characterised by chronic diarrhoea, weight loss and steatorrhoea. Laboratory abnormalities are variable, histological findings are non-specific and there is no response to a gluten-free diet. Clinical improvement after discontinuation of the drug confirms the diagnosis.

Treatment consists of discontinuation of Olmesartan, which usually results in complete resolution of symptoms. The prognosis is excellent, and follow-up endoscopy is not required if symptoms improve after withdrawal of the drug and there is no diagnostic uncertainty with another entity.

Keywords: olmesartan, enteropathy, diarrhoea.

Raúl Mendoza Rodríguez
Virgen de las Nieves Hospital. Granada.
rmendozar770@gmail.com

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Introduction

Diarrhoea is one of the most common adverse drug reactions. One of the main causes of chronic diarrhoea is coeliac disease, which is also the main cause of villous atrophy of the small intestine. However, much less frequently, there are other non-coeliac enteropathies that form a heterogeneous, extensive group characterised by diarrhoea and malabsorption.[1,2]. The drug origin of diarrhoea is a not insignificant cause of diarrhoea that must be considered in the differential diagnosis.

Angiotensin II receptor antagonists are a group of drugs widely used in the treatment of arterial hypertension, diabetic nephropathy and heart failure. Olmesartan (as one of its main representative) is a rare cause of enteropathy and should be considered in the evaluation of a patient with severe diarrhoea and weight loss.

A clinical case illustrating this association is presented below.

Clinical case

A 62-year-old woman with arterial hypertension, dyslipidaemia and grade 3A chronic kidney disease who had been on chronic treatment with Olmesartan 40 mg for five years together with Pantoprazole 20 mg and Diltiazem 120 mg. She started with diarrhoea of 15-20 bowel movements per day for three months, together with a weight loss of 12 Kg and colicky pain in the right iliac fossa, which was relieved by defecation. Her family history included a daughter with coeliac disease. Laboratory tests showed mild iron deficiency anaemia (with normal anti-transglutaminase antibodies) as well as a stool culture and Clostridioides difficile toxin test, which were negative. Upper gastrointestinal endoscopy was also requested, where macroscopically only signs of chronic gastritis were observed with duodenum with mild punctate erythema (Figure 1), and colonoscopy where three superficial ulcers were visualised in the cecum. Duodenal biopsies showed marked villous atrophy with pan-mucosal lymphocytic infiltrate and prominent intraepithelial lymphocytosis (Figures 2 & 3), and a non-specific chronic inflammatory infiltrate was found in biopsies of the cecum. It was decided to withdraw Olmesartan, after which the patient experienced a significant clinical improvement, decreasing the number of bowel movements to normal and recovering the lost weight. After two months of evolution, and taking into account the patient's family history, it was decided to perform a new ADD (Figure 4) with biopsies in which normalisation of the histological findings at the duodenal level was observed (Figure 5).

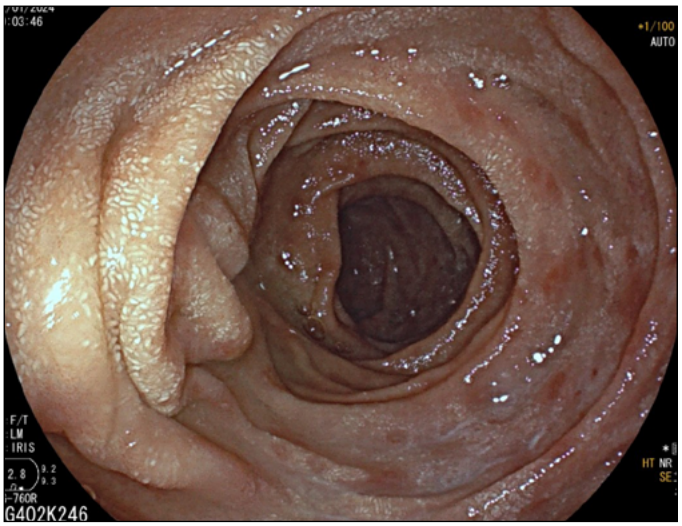

Figure 1. Second duodenal portion with mild punctate erythema, at diagnosis.

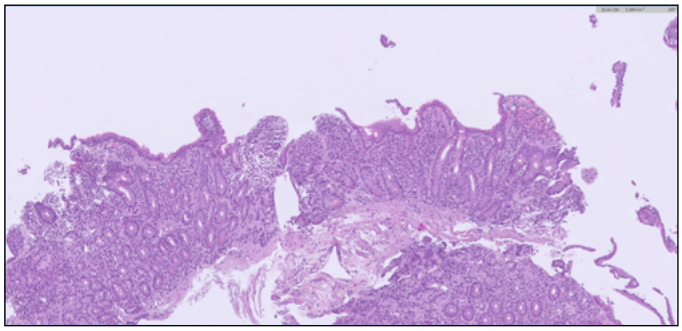

Figure 2. Endoscopic incisional biopsies of the second duodenal portion, at diagnosis. Marked villous atrophy and villous shortening with chronic panmucosal lymphocytic infiltrate.

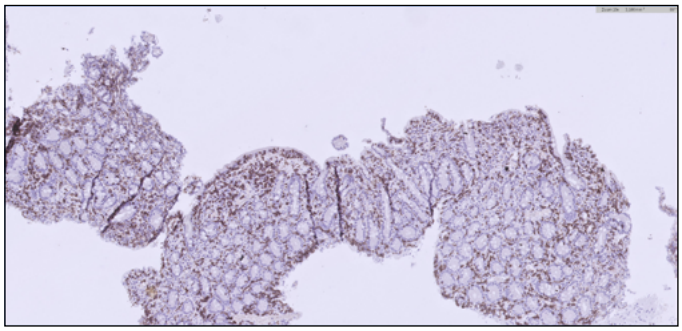

Figure 3. Endoscopic incisional biopsies of the second duodenal portion. Significant intraepithelial lymphocytosis quantified by CD3 immunohistochemistry.

Discussion

Duodenal villous atrophy with seronegative inflammatory infiltrate for celiac disease is a diagnostic challenge. Within the differential diagnosis we must consider autoimmune enteropathy, Crohn's disease, eosinophilic enteritis, giardiasis, tropical sprue, Whipple's disease, graft-versus-host disease, common variable immunodeficiency, bacterial overgrowth, neoplastic pathology (lymphomas) and drug origin (azathioprine, methotrexate, mycophenolate mofetil, etc.)[3-6].

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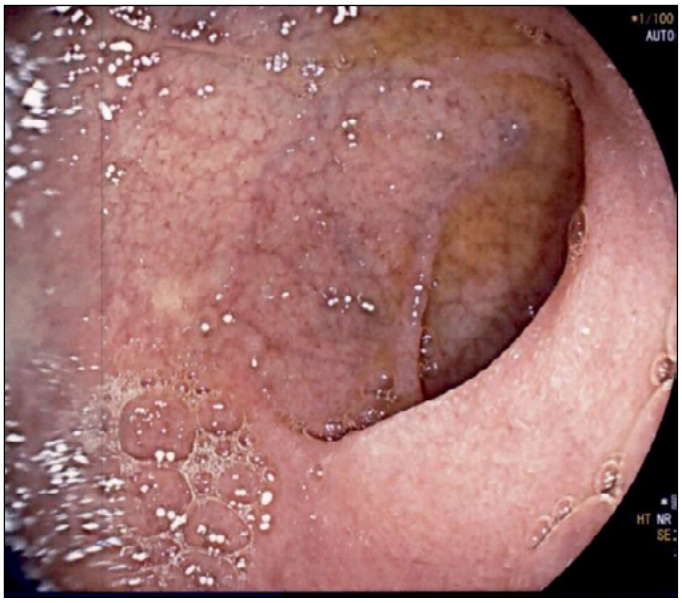

Figure 4. Second duodenal portion without notable alterations, after 2 months of Olmesartan withdrawal.

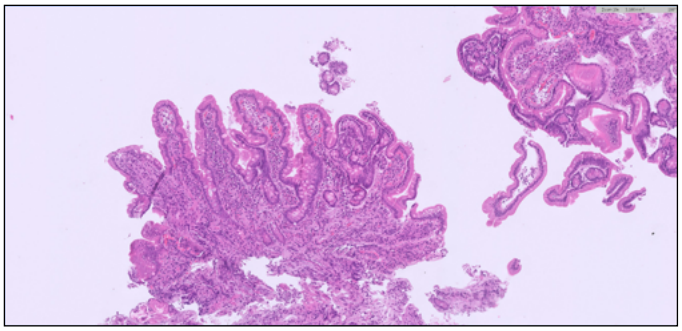

Figure 5. Endoscopic incisional biopsies of the second duodenal portion, after two months of Olmesartan withdrawal. Duodenal mucosa with preserved villous architecture, mild chronic panmucosal inflammation in the absence of intraepithelial lymphocytosis.

Since the study by Rubio-tapia J *et al* in 2012[1] in which the association between Olmesartan and enteropathy was described for the first time, and despite the fact that some studies have cast doubt on it[7], there have been numerous studies in the literature that have described this relationship[2,3,5,6,8-18].

The pathophysiological mechanisms underlying this association remain unknown. Due to the prolonged latency period between the introduction of Olmesartan and the onset of diarrhoea, it seems that the immune response involved is primarily type I. On the other hand, it appears that ARB inhibits TGF-β, a molecule involved in the maintenance of intestinal homeostasis. Furthermore, Olmesartan-associated enteropathy shares many immunological features with untreated coeliac disease, such as increased CD8+ T lymphocytes, overexpression of IL-15 or disruption of zonulin-1 protein[2,15]. Another theory postulates that majority inhibition of angiotensin type 1 (AT-1) receptors due to Olmesartan's high specificity for them, causes angiotensin to bind to the AT-2 receptor, which has a widely known pro-apoptotic function in enterocytes[6].

On the other hand, some studies suggest that Olmesartan-associated enteropathy may exhibit another endoscopic and histological phenotype related to a type I hypersensitivity reaction, with the appearance of ileal nodules with normal duodenum, as well as a monocytic and eosinophilic histological infiltrate without evidence of villous atrophy[10].

Olmesartan-associated enteropathy affects both sexes equally and occurs mainly in the seventh and eighth decades of life[4]. It is characterised by the presence of chronic diarrhoea, weight loss and steatorrhoea ,other digestive symptoms such as nausea, vomiting, bloating and asthenia may be present, the absence of coeliac-associated antibodies and no response to a gluten-free diet; in addition, histological findings of enteropathy (intraepithelial lymphocytosis, villous atrophy and subepithelial collagen deposition)[4] should be observed, which not only appear in the duodenum but can occur throughout the entire gastrointestinal tract; however, it seems that it is mainly the histological alterations in the duodenum that determine the clinical phenotype of this entity, with gastric and colonic pathological changes being of lesser importance[2]. Other causes of enteropathy must also be excluded and clinical improvement after withdrawal of Olmesartan must be demonstrated[1]. Analytical alterations are non-specific, the most frequent being the appearance of normocytic normochromic anemia and hypoalbuminaemia[4].

The mean time of enteropathy onset is 3.1 years (range 6-120 months), so it is necessary to consider this entity regardless of the time the patient has been on Olmesartan treatment[9].

The role of genetics in the pathogenesis of this entity is unknown. The presence of HLA-DQ2 and HLA-DQ8 occurs in up to 70% of patients, without this being necessary for the onset of enteropathy. Most patients are seronegative for anti-enterocyte antibodies[1,5,6].

In relation to endoscopic diagnosis, it is only necessary to perform upper gastrointestinal endoscopy in a first approach. If no endoscopic or histological alterations are found in the duodenum, colonoscopy may be considered to identify possible mucosal and histological alterations in the colon - compatible or not with this entity.

Olmesartan-associated enteropathy is not a unique adverse effect of this ARB, but has also been described in the case of Telmisartan, Valsartan and Irbesartan[2].

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Treatment of Olmesartan-associated enteropathy consists of immediate discontinuation of the drug, with all patients responding, provided that the initial diagnosis and causal association were correct, with normalisation of stools, analytical alterations and weight gain. In those rare cases where the patient shows slow improvement, some studies point to the possible usefulness of Budesonide[19].

The short and long-term prognosis of the patients is excellent, with complete cessation of symptoms when the drug is discontinued. Because of this, and in the case of an adequate response to drug cessation, it is not necessary to perform a control endoscopy to observe the resolution of the initial histological alterations, this being a cost-effective strategy.

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OBSCURE GASTROINTESTINAL BLEEDING, A DIAGNOSTIC CHALLENGE.

Villegas Pelegrina P, Navarro Moreno E, Delgado Maroto A
TORRECÁRDENAS UNIVERSITY HOSPITAL . ALMERIA.

Abstract

Small intestine or mid-gastrointestinal bleeding accounts for a small percentage of all gastrointestinal haemorrhages. Its diagnosis is possible through the use of techniques such as capsule endoscopy or enteroscopy. They are referred to as obscure in origin when the origin of the bleeding cannot be determined after upper and lower endoscopic study. Moreover, they are more challenging to manage, as the small intestine is less accessible endoscopically, and in some cases, when there is haemodynamic instability or persistent bleeding, they require joint management with interventional radiology or surgery.

Keywords: obscure gastrointestinal bleeding, small intestine, jejunal diverticulum, intraoperative endoscopy.

Introduction

A persistent or recurrent bleeding from the gastrointestinal tract, in which no origin is identified after a complete and quality gastroscopy and colonoscopy, is known as obscure gastrointestinal bleeding (OGIB). It is considered overt if the bleeding is visible in the form of rectorrhagia, haematochezia or melena, and occult when found by positive faecal occult blood test and/or iron deficiency anaemia. Only 5% of gastrointestinal haemorrhages have their origin in the small intestine, posing a diagnostic-therapeutic challenge due to the greater number of complementary tests required, thus increasing the expenditure of healthcare resources. We present a clinical case of a gastrointestinal haemorrhage in which it was necessary to go beyond gastroscopy and colonoscopy, requiring a multidisciplinary approach.

Paula Villegas Pelegrina
Torrecárdenas University Hospital. Almeria.
paulavillegaspelegrina@gmail.com

Villegas Pelegrina P, Navarro Moreno E, Delgado Maroto A. Obscure gastrointestinal bleeding, a diagnostic challenge. RAPD 2024;47(4):160-162. DOI: 10.37352/2024474.4

Clincal case

72-year-old male with a history of type 2 diabetes mellitus, dyslipidaemia, COPD and sigmoid diverticulosis. He came to the emergency department for an episode of rectorrhagia of two days' evolution, associated with syncope and food vomiting. He denied taking anti-inflammatory drugs, anticoagulants or toxic habits. On arrival he presented haemodynamic repercussions and anaemisation of five haemoglobin points. After haemodynamic resuscitation and red blood cell transfusion, gastroscopy revealed no signs of bleeding or lesions. Given the persistence of rectorrhagia and haemodynamic instability, a CT angiography was performed, but no contrast leakage was observed.

The patient was then prepared for colonoscopy, which was incomplete due to the presence of clots and fresh blood, and was repeated, this time complete, with no lesions observed. Subsequently, arteriography of the mesenteric arteries was performed, observing signs suggestive of bleeding dependent on the jejunal branch, without being able to perform any occlusive procedure. An endoscopic capsule was administered, where active bleeding in the jejunum was suspected, and finally, an intraoperative endoscopic exploration was performed, and the colonoscope was advanced to the jejunum; and surgery performed a median laparotomy, identifying several diverticula located immediately distal to the angle of Treitz. On examination of the last diverticulum, a vessel was visible at the bottom, with no active bleeding at that time. The final treatment was resection of a segment of proximal ileum and distal jejunum encompassing several diverticula, after which there were no new signs of bleeding.

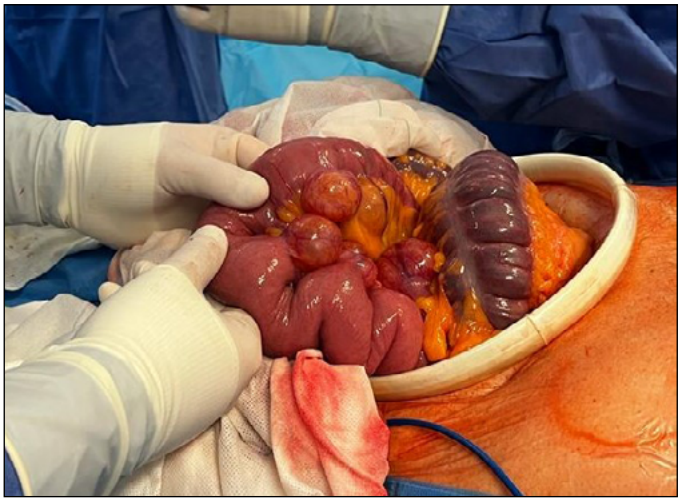

Figura 1. Several jejunal diverticula can be visualised.

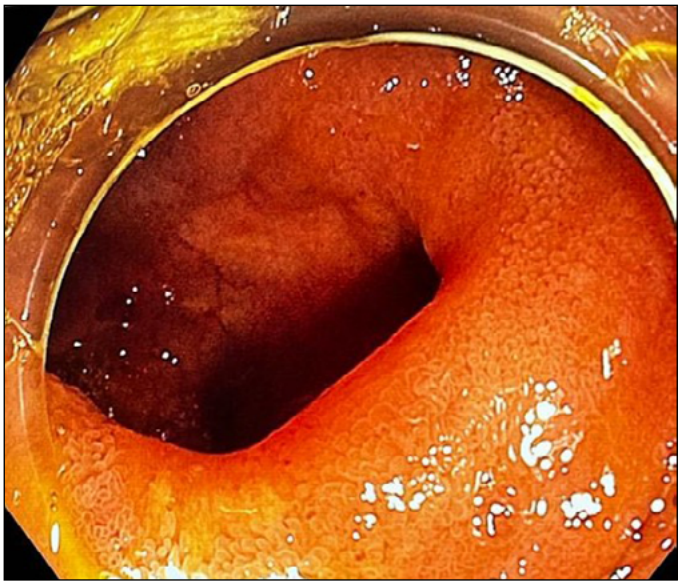

Figura 2. Jejunal diverticulum with visible vessel at the bottom.

Discussion

75% of OGIB have their origin in the small intestine, the rest are upper or lower haemorrhages that go unnoticed. The most common aetiology is vascular ectasia, especially in patients over 40 years of age and those with multiple pathologies, although in young patients tumours or Meckel's diverticulum must be ruled out. Although there are various causes, the cause of our clinical case is uncommon: small bowel diverticula.

Management will depend on the patient's condition, as the number and aggressiveness of the interventions must be in accordance with the severity of the condition and the patient's baseline condition. Few cases reach the end of the diagnostic-therapeutic algorithm, and therefore intraoperative endoscopy is rarely necessary.

If the patient is stable, capsule endoscopy is administered to identify possible causes of bleeding in the small intestine, followed by enteroscopy, either diagnostic or therapeutic. If, on the other hand, haemodynamic instability is present, arteriography is performed, usually preceded by an angio-CT scan, which can be therapeutic by means of embolisation techniques. If interventional radiology fails to control the bleeding, a deep enteroscopy is performed, in some cases even intraoperatively, to locate the bleeding point with the help of surgery, performing a laparotomy and sliding the intestinal loop over the endoscope until the origin of the bleeding is located.

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THE PANCREAS THROUGH THE SKIN: PANCREATIC PANNICULITIS, IMPORTANCE OF EARLY DIAGNOSIS

Calvo Bernal MM, Sánchez Moreno S, Cuello Entrena E, Hallouch Toutouh S
TORRECÁRDENAS UNIVERSITY HOSPITAL. ALMERIA.

Abstract

Pancreatic panniculitis (PP) is a rare cutaneous manifestation of pancreatic disease. Its evolution is parallel to the triggering process, and may precede the clinical manifestation in up to 45% of cases, so early suspicion and diagnosis is essential to improve the long-term prognosis of the disease.

Keywords: pancreatic panniculitis, pancreatitis, pancreatic cancer.

Introduction

Pancreatic panniculitis (PP) is a rare cutaneous manifestation of pancreatic processes. Its clinical presentation is indistinguishable from other types of panniculitis, so differential diagnosis with other entities is essential. The importance of its early detection lies in the fact that in up to half of the cases its appearance precedes the underlying pancreatic disease, whether benign or malignant, and it carries a worse prognosis.

Clinical case

We present the case of a 74-year-old female patient with a history of hypertension, diabetes and chronic lymphocytic leukaemia on treatment with ibrutinib, who was admitted to the hospital ward with a diagnosis of acute pancreatitis (AP) after presenting with clinical symptoms of epigastralgia associated with vomiting of four days' duration and a blood test showing hyperamylasaemia of 3,040 U/L.

On the third day of admission, the patient presented poor pain control and respiratory distress with bilateral pleural effusion. Laboratory tests showed deterioration of renal function and elevated acute phase reactants (CRP 46 mg/dL) requiring transfer to the ICU. An abdominal CT

María del Mar Calvo Bernal
Torrecárdenas University Hospital. Almeria.
marcalvobernal@gmail.com

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scan was performed showing AP and necrosis <30%, with a persistent torpid evolution, so a CT scan was requested one week later showing extensive peripancreatic necrosis and a 12 cm collection (Figure 1).

On admission, the patient presented violaceous nodular lesions on both lower limbs, painful on palpation (Figure 2), assessed by Dermatology, which performed a subcutaneous biopsy (Figure 3) with findings of panniculitis.

The patient's evolution was torpid, with progressive worsening, finally presenting multiorgan failure and *exitus* after three weeks of hospitalisation.

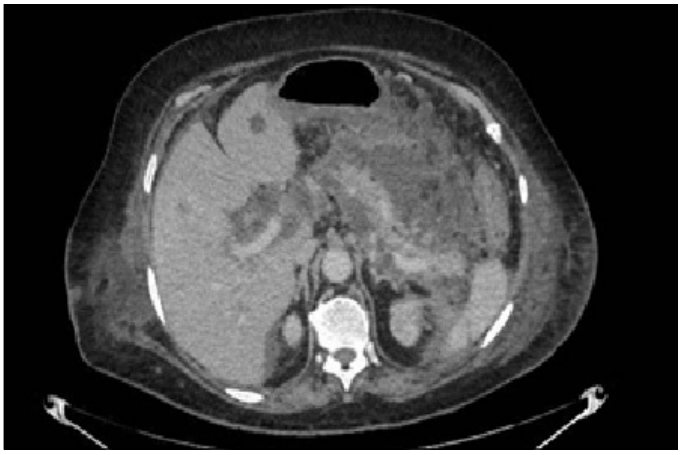

Figure 1. Abdominal CT scan. There is an increased density of peripancreatic fat with peripheral enhancement, in relation to a collection with necrotic tissue up to 12 cm in the major axis.

Discussion

PP or enzymatic necrosis of subcutaneous fat was first described by *Chiari* in 1883 in patients with acute pancreatitis. It is a rare complication of pancreatic processes, with a prevalence of 3%[1,2] and usually appears between the fourth and sixth decade of life, with a higher prevalence in males (male to female ratio 5:1).

It manifests as erythematous or purplish nodules, painful on palpation, which may spontaneously ulcerate and emit an oily material. They usually affect the lower limbs, but may also extend to the buttocks, trunk, arms and scalp. It may be associated with systemic manifestations such as fever, abdominal pain, polyarthrosis and less frequently, ascites or pleural effusion[3-6]. Its clinical course parallels that of the underlying condition and has been associated with both benign pancreatic diseases (most frequently in acute pancreatitis) and malignant diseases[2,7].

The dermal lesions are indistinguishable from other panniculitis, requiring differential diagnosis with other panniculitides, such as erythema nodosum, lupus panniculitis, sarcoidosis-related panniculitis and erythema induratum of Bazin or nodular vasculitis[1].

Diagnosis is confirmed by subcutaneous biopsy. The histopathological picture consists of lobular panniculitis with the presence of necrosis of the subcutaneous adipose tissue due to its digestion by pancreatic enzymes. Characteristic, although not pathognomonic, is the presence of necrotic adipocytes known as 'ghost cells'[2,7].

Treatment of PP is directed at the underlying pancreatic disease. Subcutaneous signs usually subside within 15-30 days after onset. Some studies suggest the use of somatostatin analogues such as octreotide to alleviate symptoms due

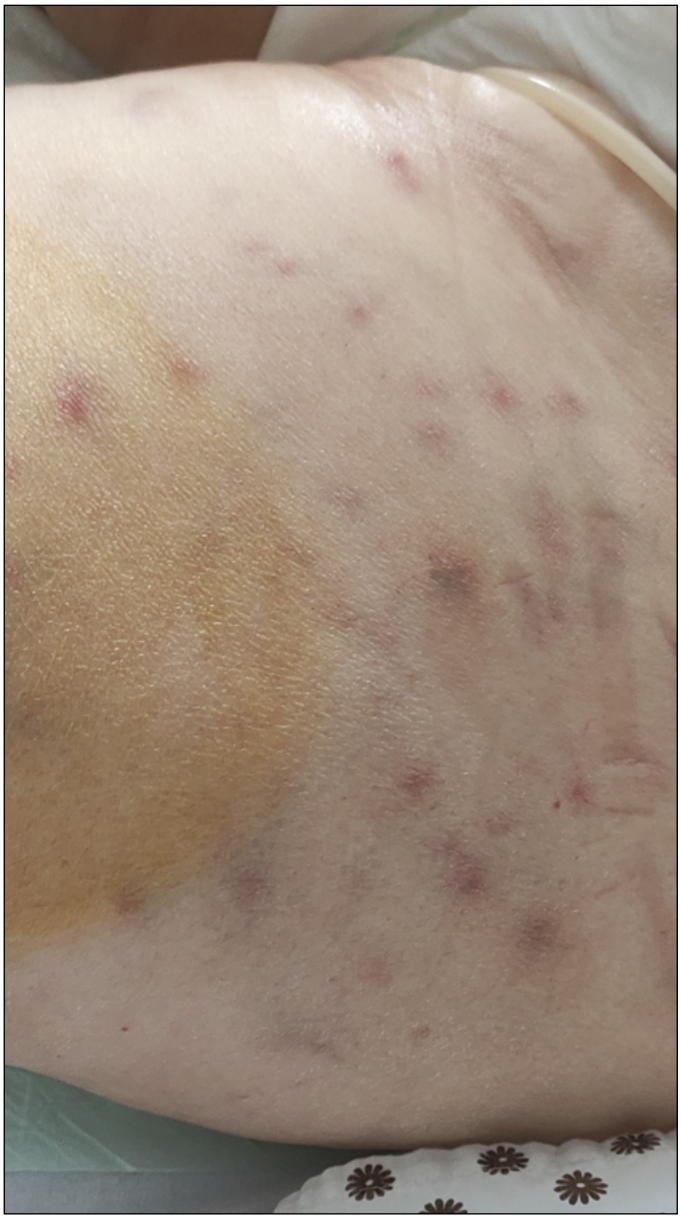

Figure 2. Photograph. Violaceous nodules on the lower limbs.

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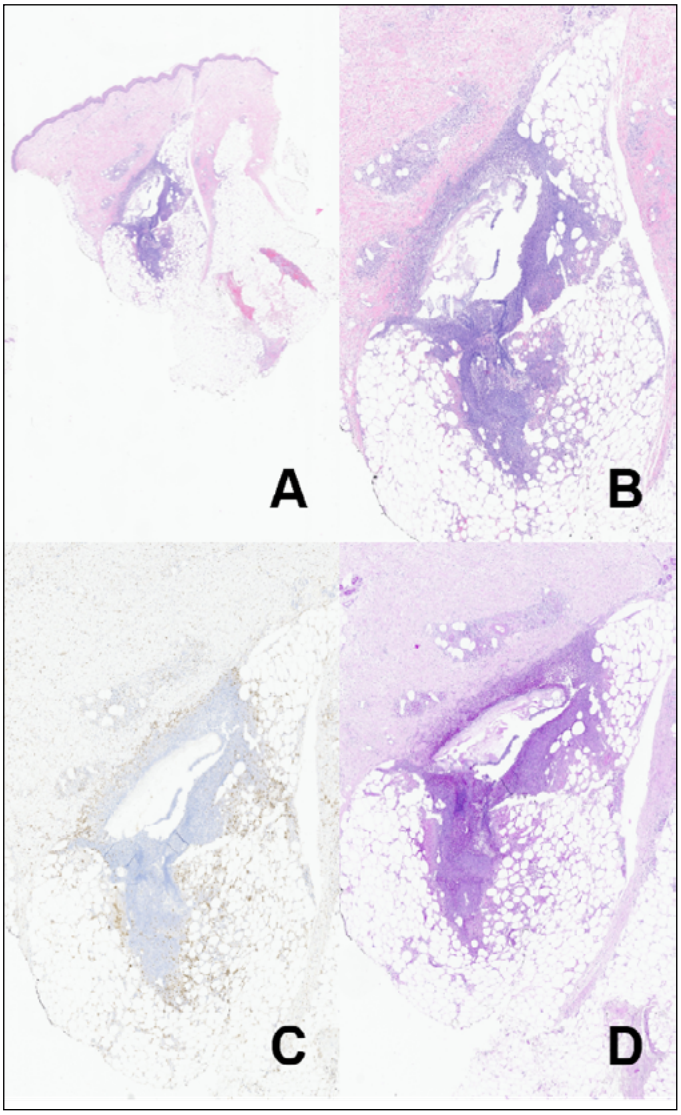

Figure 3. Pathological anatomy. A and B. Haematoxylin-eosin stain (1x and 4x). There is an area of tissue necrosis with predominantly lobular abscessation at the junction of the deep dermis with the adipose panniculus. C. CD68 stain showing the presence of a chronic inflammatory infiltrate with abundant foamy macrophages. D. PAS+ stain (4x) in the centre of the necrotic area.

to their role as inhibitors of pancreatic secretion, although experience with these drugs is limited[1,7]. The prognosis is poor in cases associated with pancreatic carcinoma.

The clinical importance of this condition derives from the fact that skin lesions usually precede clinical manifestations of pancreatic involvement in up to 45% of cases, so that the appearance of this entity obliges us to rule out pancreatic disease, even in asymptomatic patients[7]. In the case of known pancreatic patients, the appearance of this dermatosis may indicate a flare-up of a chronic condition, casting a shadow over the prognosis.

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KAYSER-FLEISCHER RING: A VISUAL SIGN OF WILSON'S DISEASE.

Plaza Fernández A, Navarro Moreno E, Sánchez García O
TORRECÁRDENAS UNIVERSITY HOSPITAL . ALMERIA.

Abstract

Wilson's disease (WD) is a rare, treatable, autosomal recessive disease which leads to pathological copper accumulation in various organs and tissues[1]. The habitual clinical manifestations include hepatic, neurological, or psychiatric symptoms, often appearing early in life[2]. A common ophthalmological finding in this disease is the Kayser-Fleischer ring, resulting from copper deposition in Descemet's membrane of the cornea[3], as illustrated in the presented clinical case.

Keywords: Wilson's disease, Kayser-Feischer ring.

Introduction

Wilson's disease (WD) is an autosomal recessive inherited disorder, rare in the general population. It is characterised by deficient biliary excretion of copper, leading to its accumulation in tissues, mainly in the liver and central nervous system, with chronic liver disease, progressive neurological disorder and psychiatric illness, with onset in early life being characteristic[1]. Another typical manifestation is ophthalmological, with the characteristic Kayser-Fleischer ring, secondary to copper deposition in Descemet's membrane of the cornea[3]. We present a case of the debut of an advanced chronic liver disease secondary to Wilson's disease with this peculiarity.

Clinical case

A 22-year-old woman from Morocco, with no personal history of interest, presented to the emergency department with one week of abdominal distension and oedema of the lower limbs, weight loss, asthenia and hyporexia. Physical examination revealed oedema of the lower limbs, moderate ascites and jaundice, with a normal neurological examination. Laboratory tests showed total bilirubin levels of 15 mg/dL, elevated transaminases (AST/ALT <2), platelets and coagulopathy. Abdominal ultrasound showed a small, heterogeneous and

Ana Plaza Fernández
Torrecárdenas University Hospital. Almeria.
anplafdez@gmail.com

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hyperechogenic liver, splenomegaly and multicompartmental ascites. Upper gastrointestinal endoscopy was performed with findings of small oesophageal varices and mild gastropathy of portal hypertension. The aetiological study was completed with negative serology and autoimmunity tests, with only low ceruloplasmin, so 24 hours urine copper test was requested. In the meantime, she was assessed by ophthalmology and the characteristic Kayser-Fleisher (KF) ring was observed (Figures 1 and 2). Finally, a cupruria of >40 mcg was obtained and the diagnosis of WD was established. Treatment with copper chelators was prescribed, with adequate tolerance, and the pre-transplant study was initiated.

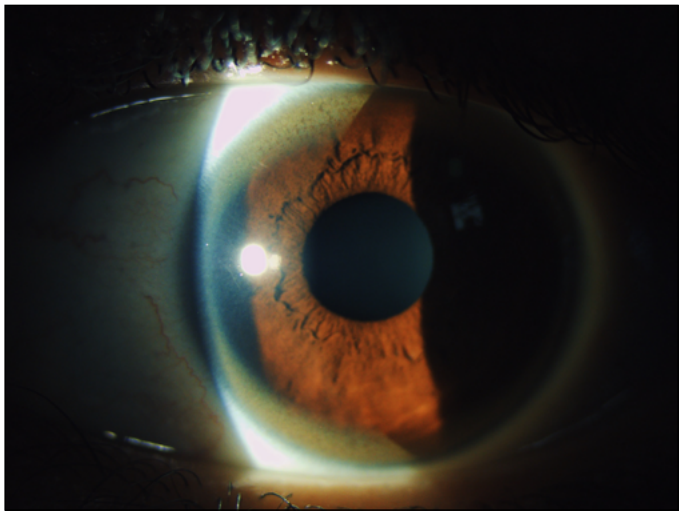

Figure 1. Kayser-Fleischer ring visible at the corneal limbus.

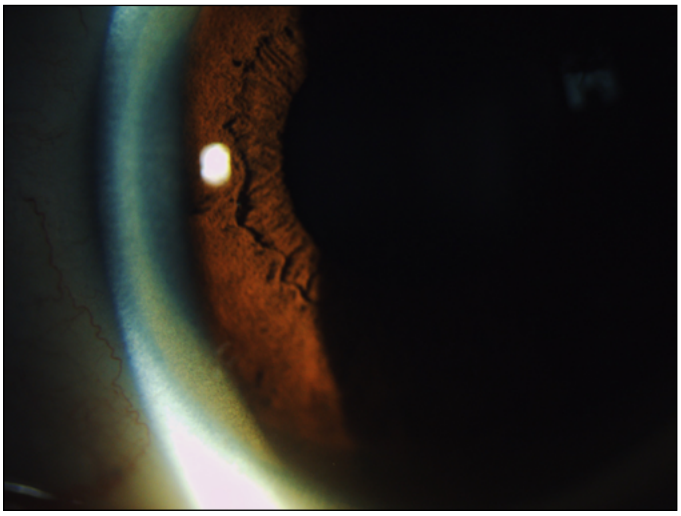

Figure 2. Kayser-Fleischer ring visible at the corneal limbus.

Discussion

Kayser-Fleischer ring is a characteristic ophthalmological finding, although not pathognomonic of WD, resulting from copper deposition in Descemet's membrane of the cornea[1]. It is present in almost all patients with WD and neurological involvement, but only in 50% with liver involvement. It also occurs in other pathologies such as primary biliary cholangitis or neonatal cholestasis[3].

Slit-lamp examination is essential for the diagnosis of Kayser-Fleischer ring, especially in the early stages[2]. They are usually asymptomatic and bilateral in onset, do not cause visual disturbances and resolve with medical treatment, 80% of them respond to chelator therapy within 3-5 years. However, they may recur with disease progression, functioning as valuable indicators of the patient's response to therapy and adherence to treatment[3].

WD is a rare but treatable inherited disorder, the early identification of which is crucial to prevent serious complications. This case illustrates the importance of a thorough diagnosis, including ophthalmological evaluation of the Kayser-Fleischer ring, a significant but not pathognomonic finding of the disease. Proper management of WD, with the use of copper chelators and continuous follow-up, can significantly improve the patient's quality of life and reduce associated morbidity and mortality. It is essential to maintain a high index of clinical suspicion and to perform a thorough evaluation in patients with unexplained liver symptoms to ensure early diagnosis and timely treatment.

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IN MEMORIAM

DR. MANUEL RODRÍGUEZ MARTÍNEZ

Dr. Manuel Rodríguez Martínez was born in Alhama de Almería on 27th december 1928 in Calle Médicos into a humble family; he spent his childhood in the towns of Gádor, La Cañada de San Urbano and Almería. He studied at the La Salle School in Almería and entered the Diocesan Seminary at a young age, where he stayed from his youth and for almost 10 years, not concluding his stay because he awoke in him another vocation of a different kind, medicine.

Although he studied philosophy and theology at the Carthusian monastery in Granada, he completed his studies at the Faculty of Medicine in the same city, later specialising in internal and emergency medicine, radiology and the digestive system at the Spanish Hospital in Mexico City, to which he devoted the rest of his life.

After his specialisation, he returned to Spain where he began his work as a doctor in home public health care professional in towns such as Rioja, Sierra Alhamilla or Pechina and later established himself as a specialist in the digestive system both in Social Security and in private medicine, practising in his practice until the age of 80, the age at which he read his long-awaited Doctoral Thesis in the Assembly Hall of the Royal Academy of Medicine of the Faculty of Granada.

Although the three pillars of his life were family, medicine and friendship, those of us who knew him well know that the most important thing in his life, in his own words, was his beloved wife **Pepita Laiz Pérez**, whom he met in 1957 in Cartagena during the university militias as a Complementary Second Lieutenant. He married her in december 1961 in the same town and with her he had 6 children, all boys, **Antonio José**, **José Manuel**, **Gonzalo Patricio**, **Miguel Ángel**, **Javier** and **Carlos**. From all of them he has 13 grandchildren and a great-granddaughter whom he met last year.

Manuel Rodríguez, Manolo for his friends, was described as a "*Renaissance man transplanted from the past*", for his vital restlessness, for his capacity and for the number of activities to which he dedicated himself throughout his life. He was a member of the Constituent Parliament of Andalusia in his first legislature with the UCD, he was President of Caja Almería (now Unicaja), of the Christian Family Movement, of the Cánovas del Castillo Foundation, of the San Buenaventura Institute, of the Tienda-Asilo charitable institution, of the Almeria Medical Union and Vice-President of the Spanish Confederation, among many other associations. He was also the founder of several others, such as the Friends of the Cathedral and the San

José Manuel Rodríguez Laiz
Mediterranean Hospital. Almeria.
jmrlaiz@gmail.com

Rodríguez Laiz JM.
Dr. Manuel Rodríguez Martínez.
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Indalecio Institute of Religious Culture, among others. He was awarded the Gold Coats of Arms and Honorary Membership of the Provincial Council and the Official College of Doctors of Almeria.

Professionally, he was awarded the Gold Medals and Honorary Membership of the **Andalusian Society of Digestive Pathology (SAPD)**, of which he was one of the founders in 1968, and the Spanish Society of Digestive Pathology (SEPD), associations of which he was president, as well as the Alumni Association of the Faculty of Medicine of Granada.

He organised and chaired more than 50 regional and national congresses and meetings throughout his professional life, including an extraordinary one of great memory for his colleagues held on a boat with a mini-cruise between the cities of Almeria, Oran and Melilla, which was a true innovation at the time and an unprecedented achievement.

He has numerous medical publications in his specialty, some others of an informative nature, as well as a biography that he published at the age of 85 called *"Almería en mi Memoria"* (Almería in my memory) where he combines memories, experiences and reflections of a life full of experiences and anecdotes. In it, he affirms his values, life, freedom and love, and as his motto "*Unum, Verum, Bonum*".

A great lover of nature, he recited by heart the Latin names of the more than 300 species that he had in *"his farmhouse"*, which was his retreat and his refuge, where he enjoyed with his family and friends.

Of deep ethical-religious, Christian, liberal and democratic convictions, he was an example of honesty, work and love for those who were close to us; of simple tastes and hobbies, familiar as the most, he always won the appreciation of those around him for his endearing disposition, his happiness transmitted and his sincere friendship. We can never thank him enough for his legacy and his example of life.

He left peacefully, in peace, without any pain and sitting next to his beloved Pepita; now he rests safely in heaven where he will be passionately organizing, as always, some meeting or trip, or perhaps he will be innovating with some topic to keep him, as always, productive and busy, surrounded by affection and friends.

Dr. José Manuel Rodríguez Laiz.

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