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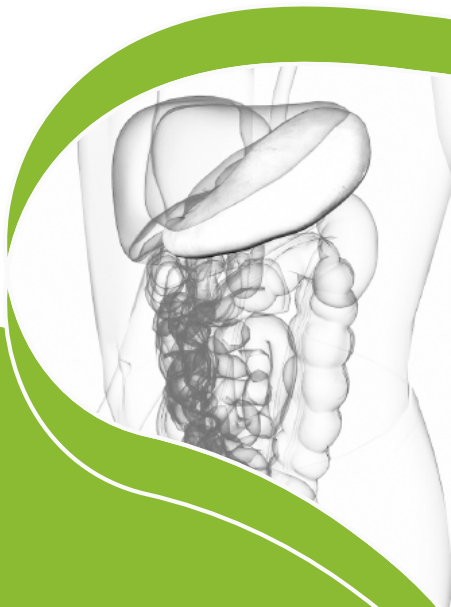
ANDALUSIAN JOURNAL OF DIGESTIVE PATHOLOGY



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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:

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1° Full title of the paper in Spanish and English
2° Surnames and first names of all authors.
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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.

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3° Centre(s) of origin (department, institution, city and country).
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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.
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- 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.

- 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:

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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).

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REVIEW ARTICLE

DOSE ESCALATION OR SWAP FOR LOSS OF RESPONSE TO BIOLOGICAL THERAPY IN IBD?

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Abstract

Biological therapies have transformed the management of inflammatory bowel disease (IBD). Nevertheless, a substantial proportion of patients experience primary non-response or secondary loss of response during treatment. This phenomenon represents a major therapeutic challenge and often requires treatment optimization strategies. Among these, dose escalation increasing dosage or interval shortening, and switching to a drug with a different mechanism of action (swap) are the most frequently considered approaches. The decision between these strategies depends on several factors, including the type of therapeutic failure, drug serum concentrations, anti-drug antibodies and the patient's clinical context. Therapeutic drug monitoring has emerged as a key tool to identify mechanisms of treatment failure and guide clinical decision-making. This article reviews the magnitude of loss of response to biological therapies in IBD, especially to anti-TNF agents, describes the underlying mechanisms and summarizes the available evidence to guide the choice between dose escalation and switching therapeutic targets.

Keywords: escalation, swap, loss of response, biological therapy, anti-TNF, inflammatory bowel disease.

Introduction

Inflammatory bowel disease (IBD) encompasses a group of chronic inflammatory disorders of the gastrointestinal tract, primarily Crohn's disease (CD) and ulcerative colitis (UC). Both conditions are characterized by a fluctuating clinical course,

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with periods of activity and remission, and by a significant impact on the quality of life of patients who suffer from them.

Over the past two decades, the treatment of IBD has undergone profound changes thanks to the development of biologic therapies and, more recently, small molecules targeting various inflammatory pathways. These advanced therapies have demonstrated significant efficacy in inducing and maintaining clinical remission, achieving mucosal healing, and reducing the need for surgery in patients with moderate-to-severe disease. However, despite these therapeutic advances, a significant proportion of patients do not respond to treatment from the outset or lose their response over time.

Primary nonresponse or primary failure is defined as the absence of clinical improvement after completing the induction phase of treatment, typically assessed between weeks 12 and 14. On the other hand, *secondary loss of response or secondary failure* is defined as the recurrence of inflammatory activity during the maintenance phase in patients who had initially responded to the drug during induction.

When we encounter a loss of response to treatment (primary or secondary), we must first confirm that the lack of improvement or clinical worsening is due to inflammatory activity in IBD. To do so, we must use surrogate markers of inflammation (fecal calprotectin, C-reactive protein) and/or tests that objectively assess this activity (ileocolonoscopy, intestinal ultrasound, enteric MRI, etc.) in clinical practice. It is essential to rule out other causes responsible for clinical worsening, such as inflammatory mechanisms unrelated to IBD (infection, ischemic colitis, vasculitis, diverticulitis, etc.) or non-inflammatory mechanisms (irritable bowel syndrome, fibrotic strictures, lactose intolerance, cancer, bile salt malabsorption, bacterial overgrowth, etc.).

This loss of response poses a significant challenge for the clinician, as it requires a reevaluation of the treatment regimen. Available strategies include intensifying treatment by increasing the dose or shortening the interval between doses of the same drug, switching to another drug within the same therapeutic class (switch), or swapping to an agent with a different mechanism of action (swap). Choosing among these alternatives requires understanding the mechanisms responsible for treatment failure and carefully assessing each patient's clinical context.

Magnitude of the problem of loss of response

Loss of response to biologic therapies is a common phenomenon in clinical practice. Several studies have evaluated treatment persistence and the long-term efficacy of anti-TNF agents in patients with IBD. In a Belgian cohort of patients treated with infliximab, Schnitzler *et al.* observed that approximately one-third of patients experienced loss of response during follow-up[1]. Similar results were reported by Karmiris et al., who analyzed the course of patients treated with adalimumab and found comparable rates of loss of efficacy[2].

Long-term studies have confirmed that this phenomenon is not uncommon. In an international multicenter analysis involving more than 1,000 patients treated with infliximab, Juillerat et al. demonstrated that a significant proportion of patients required treatment intensification or a change in medication during long-term follow-up[3]. Overall, the incidence of loss of response to anti-TNF agents is estimated to range from 15% to 20% per patient-year[4].

Another interesting aspect is understanding when loss of response occurs over time. This risk of loss of response appears to be higher during the first year of treatment. Schultheiss et al. observed that the incidence of loss of response was higher during the first year (17.2% patient-years) and decreased significantly over time, to 4.8% after four years. The first year of exposure to anti-TNF was also associated with a significantly higher risk of treatment intensification or discontinuation; these events decreased as the duration of treatment increased. In fact, patients in this cohort who maintained a response for ≥2 years had a low risk of subsequent loss of response [5]. This finding suggests that mechanisms of immunogenicity and pharmacokinetic variability may play an important role in the early phases of treatment. Predictive factors associated with loss of response to anti-TNF include UC (vs. CD) and the stenotic and fistulizing phenotype of CD.

Although non-anti-TNF biologics may also experience loss of response, some registries suggest that their treatment persistence may be higher. In an Australian database that included more than 1,000 advanced treatment regimens, Ko *et al.* observed differences in persistence among different classes of biologic treatments, with significantly lower persistence for anti-TNF drugs[6]. However, the available evidence is still limited, and further comparative studies are needed.

Mechanisms of loss of response

Loss of response to biologic treatments can be explained by various pharmacological and pathophysiological mechanisms. Traditionally, three main types of treatment failure are distinguished: pharmacodynamic, pharmacokinetic, and immunogenic.

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Pharmacodynamic failure occurs when the patient has adequate serum levels of the drug, but the disease remains active. In this context, blocking the specific inflammatory pathway is not sufficient to control disease activity. This phenomenon reflects the complexity of the immune networks involved in IBD, where multiple cytokines and signaling pathways contribute to the inflammatory process.

Pharmacokinetic failure is characterized by subtherapeutic serum levels of the drug in the absence of anti-drug antibodies. This phenomenon may be due to multiple factors, including increased drug clearance, an increased volume of distribution, or intestinal losses associated with severe inflammation. In these cases, optimizing treatment by increasing the dose or shortening the dosing interval can restore adequate therapeutic concentrations.

Finally, ***immunogenic failure*** occurs when the patient's immune system generates antibodies directed against the biologic drug. These antibodies can neutralize its effect or accelerate its elimination, reducing its clinical efficacy. Immunogenicity has been reported most frequently with anti-TNF therapies, especially when used as monotherapy.

Although pharmacokinetic failure was traditionally considered the most common (51%), followed by pharmacodynamic failure (30%) and immunogenic failure (19%)[7]; updated data from the Leuven group estimate pharmacodynamic failure to be the primary mechanism of loss of response (73%), followed by immunogenic failure (16%) and pharmacokinetic failure (11%)[8]. Understanding these mechanisms is essential for selecting the most appropriate therapeutic strategy. In this context, therapeutic drug monitoring has taken on a central role in the management of IBD, serving as a tool that allows for a better understanding of the causes of loss of response and improves clinical decision-making.

Therapeutic strategies for loss of response: clinical scenarios.

Once loss of response has been confirmed and other causes of clinical worsening have been ruled out, the physician must choose among different therapeutic strategies. The two main options are treatment intensification or a change in mechanism of action.

Primary failure

The key to reducing primary failure with anti-TNF therapy is optimizing the drug during the induction phase. The prospective study PANTS evaluated the relationship between serum levels of infliximab and adalimumab during the induction phase and long-term clinical outcomes. The authors observed that patients with higher levels after induction (measured at week 14) were more likely to maintain clinical remission throughout follow-up, at week 54[9]. Therefore, measuring post-induction levels could help identify subgroups of patients who would benefit from early drug intensification.

Based on these data, target concentrations have been proposed for different drugs. Although there are no clearly defined therapeutic thresholds, during the induction phase it is recommended to achieve levels of approximately 7–10 µg/ml for infliximab and levels above 10–12 µg/ml for adalimumab[10,11]. These concentrations have been associated with better clinical outcomes, higher long-term remission rates, and a greater likelihood of mucosal healing.

Another important aspect to consider during this initial or induction phase—and one that is closely linked to the previous point—is immunogenicity. One important concept is that anti-drug antibodies develop during anti-TNF induction therapy; these are not detected by standard drug-sensitive assays but are detected by drug-tolerant assays capable of identifying antibodies in the presence of the drug. In this context, Tournier *et al*[12] reported on a cohort of 108 patients with ulcerative colitis (UC) and Crohn's disease (CD) treated with adalimumab and infliximab, in whom anti-drug antibodies were detected by week 2. They observed that patients who developed anti-drug antibodies early (week 2) had a less favorable outcome, with higher rates of treatment discontinuation due to loss of response at 6 months compared to patients who did not develop antibodies; this was true for both those treated with infliximab and those treated with adalimumab. Therefore, the ability to monitor drugs using drug-tolerance tests would allow us to detect antibodies early and identify subgroups of patients at risk for drug loss in the following months.

The reason for discontinuing the first anti-TNF drug determines the success of the second anti-TNF drug. And among the various causes, primary failure is associated with the worst remission rates achieved with the second anti-TNF agent—around 34% compared to 41% if the reason for discontinuing the first anti-TNF agent is secondary failure, or 78% if the first agent was discontinued due to intolerance[13].

Furthermore, primary failure not only has a negative impact on the benefit of the second anti-TNF agent but also represents the situation in which we will achieve the least benefit from other non-anti-TNF biologics in second-line or subsequent treatments, as it results in a 25% lower response

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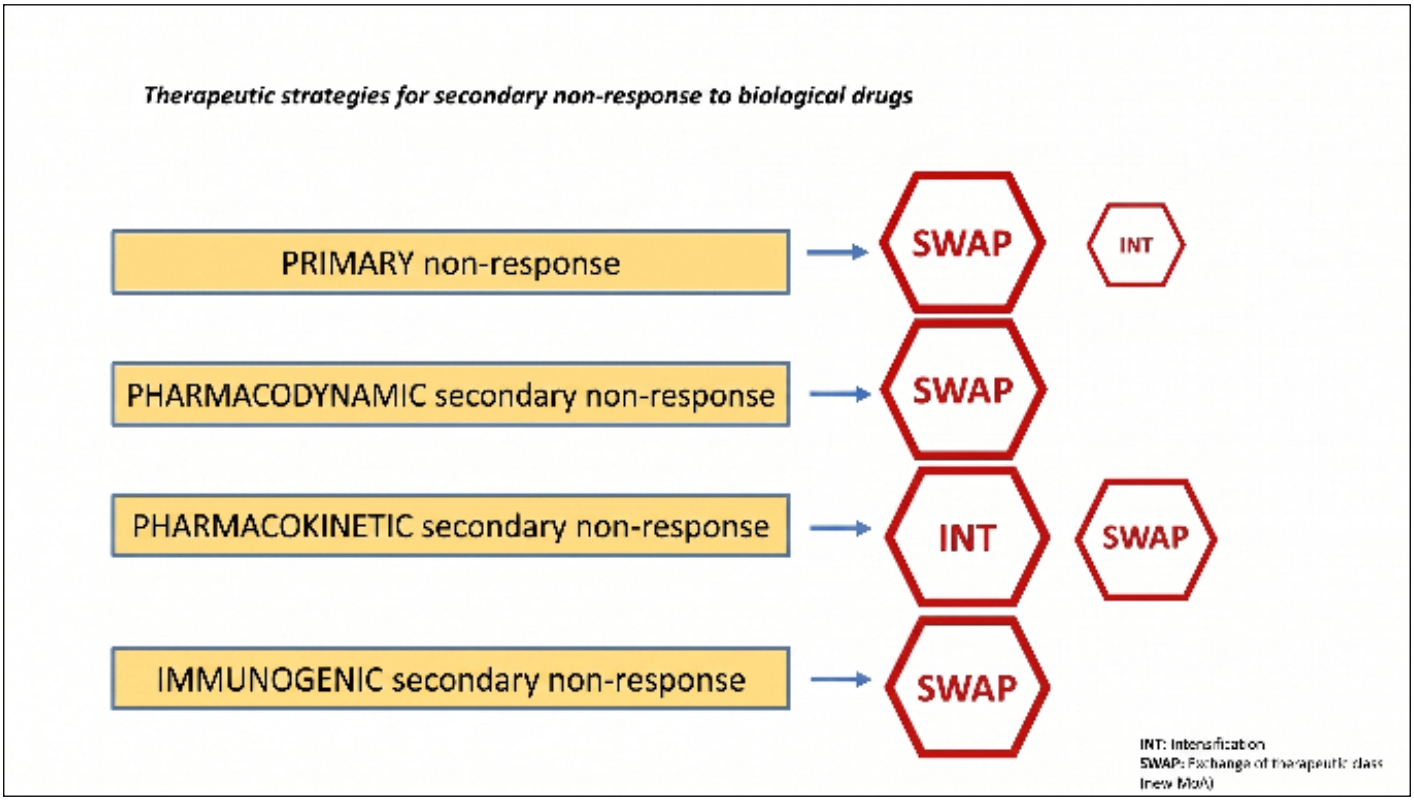

Figure 1. ***Therapeutic strategies in the event of loss of response to biologic drugs.***

rate in second-line therapy compared to secondary failure or intolerance[14]. It would seem reasonable to consider, for this second biologic indicated following primary failure of the first anti-TNF agent, higher induction doses, combination with an immunosuppressant, and early proactive optimization.

Therefore, in the event of primary failure, the swap strategy would, a priori, provide the greatest benefit, while evaluating the possibility of intensification in certain situations—especially if we have the capacity to monitor post-induction levels with the ability to detect anti-drug antibodies.

Secondary pharmacodynamic failure (therapeutic levels)

In this situation, where the patient has adequate therapeutic levels but inflammatory activity persists, intensification is usually ineffective. In such cases, switching to a drug with a different mechanism of action (swap) may yield better results. Yanai et al. demonstrated that patients with adequate therapeutic levels of anti-TNF were significantly less likely to regain response through dose escalation (30%) compared to those who switched to a drug with a different mechanism of action (68%)[15].

Roblin *et al.*[16] compared these two strategies (intensification vs. swap) in patients who had lost response to adalimumab while maintaining therapeutic levels. At 24 months, treatment discontinuation was 14.8% in the swap group compared with 59.6% in the adalimumab intensification group. Furthermore, the time to treatment discontinuation was significantly longer following the drug switch (>24 months vs. 13.3 months).

Therefore, in patients with IBD who experience a secondary loss of response of pharmacodynamic origin, switching to a biologic with a different mechanism of action is more effective than optimizing the dose of the same drug.

Secondary pharmacokinetic failure (low levels, Acs -)

Yanai *et al.* also evaluated this clinical scenario by comparing two strategies—intensification of the same anti-TNF agent versus switching to another anti-TNF agent—in a cohort of 247 patients. The percentage of patients who regained a response was significantly higher in the intensification group compared to the switch group (38% vs. 0%). Therefore, this intensification strategy is particularly effective in patients with low serum drug levels and no anti-drug antibodies, as it

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can restore adequate therapeutic concentrations and regain clinical response.

The next question regarding this optimization strategy is which intensification approach is more beneficial: increasing the dose or shortening the dosing interval. In general, combining both approaches—increasing the dose and shortening the dosing interval—is best. However, when analyzing both strategies independently, it appears that doubling the dose yields greater benefits than shortening the interval[17]. This approach of doubling the dose may seem counterintuitive at first glance, as it results in higher peak levels but lower trough levels. However, it is believed that the formation of anti-drug antibodies is suppressed when anti-TNF concentrations reach a certain threshold, at which point a state of tolerance is achieved; this threshold would be reached more easily with higher concentrations, which can be achieved by doubling the dose.

The drug levels to be achieved following dose escalation are not clearly defined and will depend on the desired treatment goals. More ambitious goals, such as mucosal healing, will require greater drug exposure and, therefore, higher concentrations than a less demanding goal such as clinical remission. Special situations, such as perianal disease, require even higher drug levels to achieve remission. In general, we could consider infliximab levels >8 µg/ml and adalimumab levels >12 µg/ml.

Another issue of great interest is determining how long to continue the intensification strategy. Although intensification is an effective strategy in this context of secondary loss of response, a subgroup of patients may not respond to intensification (tertiary nonresponse) or may not maintain a durable response with intensification (tertiary loss of response). A systematic review and meta-analysis[18] evaluates this response to anti-TNF intensification. A response to intensification (tertiary response) was more likely than a non-response within the first 6 months (RR 2.58; 95% CI 1.76–3.79). However, beyond 6 months, the probability of sustained response versus loss of response was similar (RR 1.10; 95% CI 0.75–1.61).

Non-response to intensification (tertiary non-response) occurred in up to 45% of patients within the first 6 months after intensification, while loss of response to intensification (tertiary loss of response) beyond 6 months was observed in up to 64% of patients. Given these results, it seems reasonable not to unnecessarily prolong the intensification strategy, to conduct an early evaluation of it—especially at 6 months—and to consider changing the strategy if no response is achieved.

Secondary immunogenic failure (low levels, Acs +)

The development of anti-drug antibodies represents another common scenario. The presence or formation of antibodies occurs primarily during the first 12 months, after which the curve levels off. Most non-transient antibodies are produced during this first year, and these are the ones associated with loss of response. Hence the importance of determining drug levels after induction, even during clinical remission; in this scenario, subtherapeutic levels could be associated with an increased risk of antibody formation and heightened inflammatory activity.

When these anti-drug antibodies are detected at high levels, the likelihood of regaining a response through dose escalation is low; therefore, switching to another biologic treatment (swap) is generally recommended.

Often, the pharmacokinetic profile of the first anti-TNF agent is replicated with the second anti-TNF agent, and antibodies against one anti-TNF agent predispose patients to the development of antibodies against the second anti-TNF agent. Therefore, the strategy of switching to a second anti-TNF agent following immunogenic failure with the first anti-TNF agent would not be more beneficial than switching to a drug with a different mechanism of action (swap).

When should a second anti-tnf be used after failure of the first anti-tnf?

In certain patients, the use of a second anti-TNF may be considered after failure of the first. However, in general, the benefit of switching to a second anti-TNF is less than that of switching to a drug with a different mechanism of action. Several studies have shown that the efficacy of a second anti-TNF agent depends largely on the cause of failure of the first. Gisbert et al. observed that patients with primary failure of the first anti-TNF agent had significantly lower remission rates after switching to a second anti-TNF agent[13].

Furthermore, the presence of antibodies against an anti-TNF drug may increase the risk of developing antibodies against a second drug in the same class. In this context, some authors recommend the concomitant use of immunosuppressants with this second anti-TNF drug to reduce immunogenicity and improve treatment adherence.

Therefore, this strategy may be effective when discontinuation of the first drug is due to adverse effects. In any case, it will depend on the therapeutic indication and

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the likelihood of response to other treatment options, as is the case with specific conditions such as perianal disease, extraintestinal manifestations, etc.

Therapeutic strategies for loss of response to non-anti-tnf biologics

The introduction of biologics with mechanisms of action different from those of anti-TNF agents has significantly expanded the therapeutic options available to patients with IBD. Notable among these are ustekinumab, vedolizumab, drugs targeting the interleukin-23 pathway (risankizumab, mirikizumab, and guselkumab), and JAK inhibitors.

Although the evidence regarding the management of loss of response to these drugs is substantially less than that available for anti-TNF agents, we do have data on treatment optimization, particularly for ustekinumab and vedolizumab. Although the utility of monitoring drug levels appears to be lower compared to anti-TNF agents, most studies reiterate the concept that higher drug exposure, higher serum concentrations of the drug, and a greater likelihood of achieving therapeutic outcomes—both clinical and endoscopic—go hand in hand.

Ustekinumab has demonstrated efficacy in both UC and CD. However, some patients also experience loss of response during treatment. This meta-analysis of 14 studies[19] evaluated loss of response to ustekinumab. In UC, the annual risk of loss of response to this drug was 21% patient-years, with approximately 25% of patients requiring a dose escalation during follow-up. Treatment intensification allowed for the restoration of clinical response in 58% of patients who had experienced a secondary loss of response. In ulcerative colitis, data are limited, although approximately 35% of patients required dose adjustment in the only available study.

Among the strategies for optimizing ustekinumab reported in the literature that allow for the restoration of response in a proportion of patients are intensification (shortening the dosing interval to every 4 or 6 weeks), intravenous maintenance every 4 weeks, and reinduction. However, two recent trials question the utility of optimizing ustekinumab in the event of loss of response. The POWER study[20] is a randomized clinical trial that evaluated intravenous (IV) reinduction of ustekinumab in patients who experienced a secondary loss of response during maintenance with the subcutaneous formulation every 8 weeks; patients were randomized to either IV reinduction or continued subcutaneous maintenance. Outcomes were assessed at 16 weeks, and no significant differences in clinical response were found between the two treatment arms. However, better endoscopic and biological outcomes were achieved with intravenous reinduction.

The REScUE study[21] is a double-blind, randomized, placebo-controlled trial that evaluated, in patients with Crohn's disease who had lost response to ustekinumab, whether intensifying treatment every 4 weeks provided additional benefit compared with continuing the drug every 8 weeks. At week 48, the rates of corticosteroid-free clinical remission, biological remission, and endoscopic response and remission showed no significant differences between the two arms.

These results call for a reevaluation of the utility of optimizing the ustekinumab dose in routine clinical practice in favor of more effective treatment strategies.

In cases of loss of response to vedolizumab, intensifying treatment by shortening the dosing interval or using weekly subcutaneous formulations may be effective. Recent results are available from the PRIVEDO study[22], a prospective study that evaluated two maintenance strategies in patients with a partial response to intravenous (IV) induction with vedolizumab: subcutaneous vedolizumab 108 mg every 2 weeks versus intensification of IV vedolizumab every 4 weeks. Steroid-free clinical remission with normalization of fecal calprotectin was significantly higher with subcutaneous maintenance at week 26 (57% vs. 25%, $p < 0.001$) and week 52 (48% vs. 25%, $p = 0.016$).

The OPTI-VEDO study[23] is a multicenter study that evaluates the intensification of subcutaneous vedolizumab to a weekly regimen following a secondary loss of response to subcutaneous vedolizumab administered every 2 weeks. With this optimization strategy, a corticosteroid-free clinical response was achieved at 3 months in 35% of patients with ulcerative colitis (UC) and 43% of those with Crohn's disease (CD), with secondary loss of response being the primary predictor of response to intensification (vs. primary nonresponse, OR 5.8).

Although clinical experience is still limited regarding optimization strategies for drugs such as risankizumab or JAK inhibitors like upadacitinib, some studies suggest that reinduction or intensification of treatment may restore the response in a considerable percentage of patients.

In the case of mirikizumab, the prescribing information includes optimization strategies such as extended induction with three additional intravenous doses starting at week 12 for patients with a partial response to induction, or reinduction with three intravenous doses for patients who lose response during maintenance therapy.

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Recently, a new selective IL-23 inhibitor, guselkumab, has been approved; it has demonstrated efficacy in patients with moderate-to-severe active CD and UC. Although long-term data on loss of response and the need for dose escalation are not yet available, the prescribing information outlines a strategy for optimizing this medication with a maintenance dose of 200 mg every 4 weeks starting at week 12 for patients who, in the clinician's judgment, have not achieved an adequate therapeutic benefit following induction therapy.

Conclusions

Loss of response to biologic therapies remains one of the main challenges in the management of inflammatory bowel disease. Although therapeutic advances have considerably expanded the available options, treatment optimization remains a common strategy for maximizing clinical benefits. Therapeutic drug monitoring plays a key role, especially with anti-TNF agents, in identifying the mechanisms of treatment failure and in selecting the most appropriate strategy for each patient. In general, switching to a drug with a different mechanism of action (swap) is the most favorable strategy in most situations, particularly in cases of primary failure, secondary pharmacodynamic failure, or immunogenic failure. Treatment intensification is particularly useful in cases of pharmacokinetic failure.

As more evidence becomes available on new biologics and small molecules, it will be possible to define more precisely the optimal strategies for managing loss of response and improving long-term outcomes in patients treated with these drugs.

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REVIEW ARTICLE

AUTOIMMUNE HEPATITIS: MANAGEMENT OF COMPLEX CASES.

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Abstract

Autoimmune hepatitis (AIH) is a chronic immune-mediated inflammatory liver disease that may progress to cirrhosis, hepatic decompensation, and liver transplantation if not adequately controlled[1,2]. Although standard therapy with corticosteroids and azathioprine (AZA) induces remission in the majority of patients, approximately 10–30% develop complex disease courses characterized by treatment intolerance, insufficient response, or severe acute presentations[1,3]. The primary therapeutic goal is to achieve complete biochemical response (CBR), defined as normalization of serum transaminases and immunoglobulin G (IgG) levels, ideally within 6 months[4]. This review addresses the management of refractory AIH, the use of second- and third-line therapies, and specific considerations in special populations, including pregnant women and patients with decompensated cirrhosis or metabolic dysfunction–associated steatotic liver disease (MASLD).

Keywords: autoimmune hepatitis, complete biochemical response, refractory disease, second- and third-line therapy, mycophenolate mofetil, complex cases.

Introduction

AIH is an immune-mediated disease that affects people of all ages and ethnicities, with a marked predominance in women[5]. It is characterized by the presence of autoantibodies, IgG hypergammaglobulinemia, and interfacial hepatitis on histology[1,6]. Its clinical spectrum is broad, ranging from indolent forms to severe acute presentations with coagulopathy and a

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risk of liver failure. Without treatment, mortality is high, up to 6 times higher in the first year[5]. Conventional management is based on induction with corticosteroids (prednisolone or budesonide) followed by maintenance therapy with AZA[7,8]. However, clinical heterogeneity and drug toxicity necessitate therapeutic personalization to prevent progression to cirrhosis and the need for transplantation[2,6]. This clinical heterogeneity explains why a significant percentage of patients do not fit the classic therapeutic paradigm, constituting so-called complex cases, whose management remains a significant clinical challenge.

We present a narrative review based on recent guidelines (EASL 2025), position statements, and relevant observational studies and clinical trials. We will also use the definitions and terminology established by the International Autoimmune Hepatitis Group (IAIHG).

Definition of complex cases

In the context of AIH, we can define "complex cases" as patients who present significant challenges in diagnosis or management, who often require second- or third-line treatments, or who have specific clinical features or comorbidities that complicate standard treatment[1,8-10].

Complex cases can be grouped into one of the following categories, whose definitions are summarized in table 1:

1. **Inadequate response or disease refractory to standard treatment.** The standard first-line treatment for AIH consists of corticosteroids (with or without AZA)[1,3,10]. When this treatment fails, the case is considered complex or "difficult to treat".

1.1. Inadequate response or lack of response: A considerable proportion of patients (approximately 10–25% of cases according to older studies, or about one-third overall) develop an inadequate or no response to standard therapy[1,3,6,11]. An inadequate response is defined as the absence of CBR (normalization of serum transaminases and IgG below the upper limit of normal (ULN)) within 6 months of treatment initiation[1,4]. Primary nonresponse is defined as a decrease of less than 50% in serum transaminases within 4 weeks of treatment initiation[4].

1.2. Refractory disease: This refers to a subgroup of patients who, even after receiving second-line treatments (such as mycophenolate mofetil, MMF), still have active disease. These patients are the most likely to develop long-term complications, such as decompensated cirrhosis and hepatocellular carcinoma[1], and are candidates for third-line therapies, including calcineurin inhibitors such as tacrolimus or cyclosporine, or biologic agents such

Domain	Operational Criterion	Practical Implication
Insufficient response	No complete biochemical response (CBR) at 6 months	Review adherence and diagnosis; optimize therapy and consider second-line treatment
Primary nonresponse	<50% reduction in transaminases at 4 weeks	Urgent reassessment; exclude alternative diagnoses; intensify treatment
Refractory disease	Persistent disease activity despite second-line therapy	Third-line therapy/biologics at an expert center; consider transplantation if advanced disease
Intolerance	Adverse event requiring treatment discontinuation	Switch to an alternative agent (6-MP/MMF/budesonide, as appropriate)
Acute/severe presentations	asAIH/ALF/ACLF	Early corticosteroid trial and use of dynamic transplant criteria
Overlap syndromes	AIH/PBC or AIH/PSC	Treat the dominant component; combination therapy if response is suboptimal
Special populations	Pregnancy, decompensated cirrhosis, MASLD	Careful benefit–risk assessment; individualized management decisions
Adherence/psychosocial factors	Nonadherence or treatment barriers	Educational interventions; monitor metabolites; simplify treatment regimen

Notes: CBR: complete biochemical response (ALT/AST and IgG < ULN). asAIH: acute severe autoimmune hepatitis. ALF: acute liver failure. ACLF: acute-on-chronic liver failure.

Table 1. ***Operational Definition of a "Complex Case" in Autoimmune Hepatitis.***

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as rituximab or tumor necrosis factor alpha (anti-TNF-α) blockers[1,10].

2. **Treatment intolerance.** Cases are also considered complex when the patient develops intolerance to standard medications, necessitating a change in the therapeutic regimen[1,6,10]. Treatment intolerance is defined as any adverse event possibly related to the immunosuppressive regimen that leads to the potential withdrawal of the drug[4,5].

2.1. Azathioprine intolerance: Intolerance or an inadequate response to AZA occurs in approximately 10–25% of cases. MMF is considered an effective and safe second-line alternative in these patients[2].

2.2. Side effects of corticosteroids: Long-term use of corticosteroids is associated with significant adverse effects, necessitating the use of non-steroidal or low-dose maintenance therapies[5,11].

3. **Specific clinical presentations and comorbidities**. Certain clinical scenarios and patient subgroups make management inherently more complex, often requiring a personalized treatment approach[2,6].

3.1. Acute and severe forms. AIH can manifest as acute liver failure (ALF), with encephalopathy, or as severe acute (asAIH), with jaundice and coagulopathy (INR >1.5 and <2) but without encephalopathy [5,11]. Acute-on-chronic liver failure (ACLF) may also occur, in which acute injury develops on top of advanced liver disease accompanied by extrahepatic organ failure[5]. These presentations carry a high risk of requiring a liver transplant (LT) and demand rapid decision-making[10,11].

3.2. Overlap syndromes. The coexistence of AIH with other autoimmune liver diseases, such as primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC), complicates diagnosis and treatment[6,8,10]. In children, autoimmune sclerosing cholangitis (ASC) or overlapping AIH/PSC is particularly common, affecting up to 50% of pediatric patients with features of AIH[10,12].

3.3. Drug-induced autoimmune-like hepatitis (DI-ALH). This condition resembles classic AIH in terms of serological and histological markers, which poses a diagnostic challenge. Distinguishing it from AIH is crucial, as DI-ALH requires only brief immunosuppressive therapy and should resolve with the withdrawal of the causative agent[5,10].

3.4. Challenges in specific populations or those with comorbidities: such as management in pregnant women, who often require close multidisciplinary care[5], patients with AIH and decompensated cirrhosis, who likely require evaluation for LT[5,6], obesity and metabolic syndrome, where the need for high-dose steroids presents significant challenges in these patients due to the risk of adverse effects such as weight gain and steroid-induced hyperglycemia[2], as well as worsening of the metabolic component in patients with MASLD[5,8,10]. Lack of adherence; noncompliance with treatment (common in adolescents and young adults) is considered a challenge that may require strategies such as the use of rituximab to ensure periodic administration in a controlled setting[2,12].

3.5. Management of lack of response to standard treatment

This occurs when there is an inadequate response or a primary lack of response to treatment with corticosteroids and AZA. In some patients, the response to treatment may be slower and take up to 12 months, although a lack of CBR at 6 months is a predictor of adverse long-term outcomes[5,13].

In these situations, the first step is to **confirm adherence**. Nonadherence to treatment is the most common cause of treatment failure, especially in adolescents and young adults[5,12]. Adopting a holistic approach that considers the emotional impact the disease may have on the patient can help us understand the fears or difficulties they may face in coping with the disease and its treatment[5]. It is highly recommended to measure azathioprine metabolites (Figure 1), specifically 6-thioguanine (6-TGN), since very low or undetectable levels confirm non-compliance with the medication[1,5,12].

It is also worth **re-evaluating the initial diagnosis** and considering other conditions that present with persistently elevated transaminases, such as hepatitis E, Wilson's disease, or drug-induced liver injury (DILI), among others[5,12].

Once adherence and the diagnosis are confirmed, the next step is to optimize treatment. To do this, we must adjust the dose of thiopurines, and in this regard, measuring metabolites remains extremely helpful. In patients with 6-TGN levels below 220 pmol/8×10^8 erythrocytes, the azathioprine dose should be increased to 2 or 2.5 mg/kg[1,5,12]. We must also

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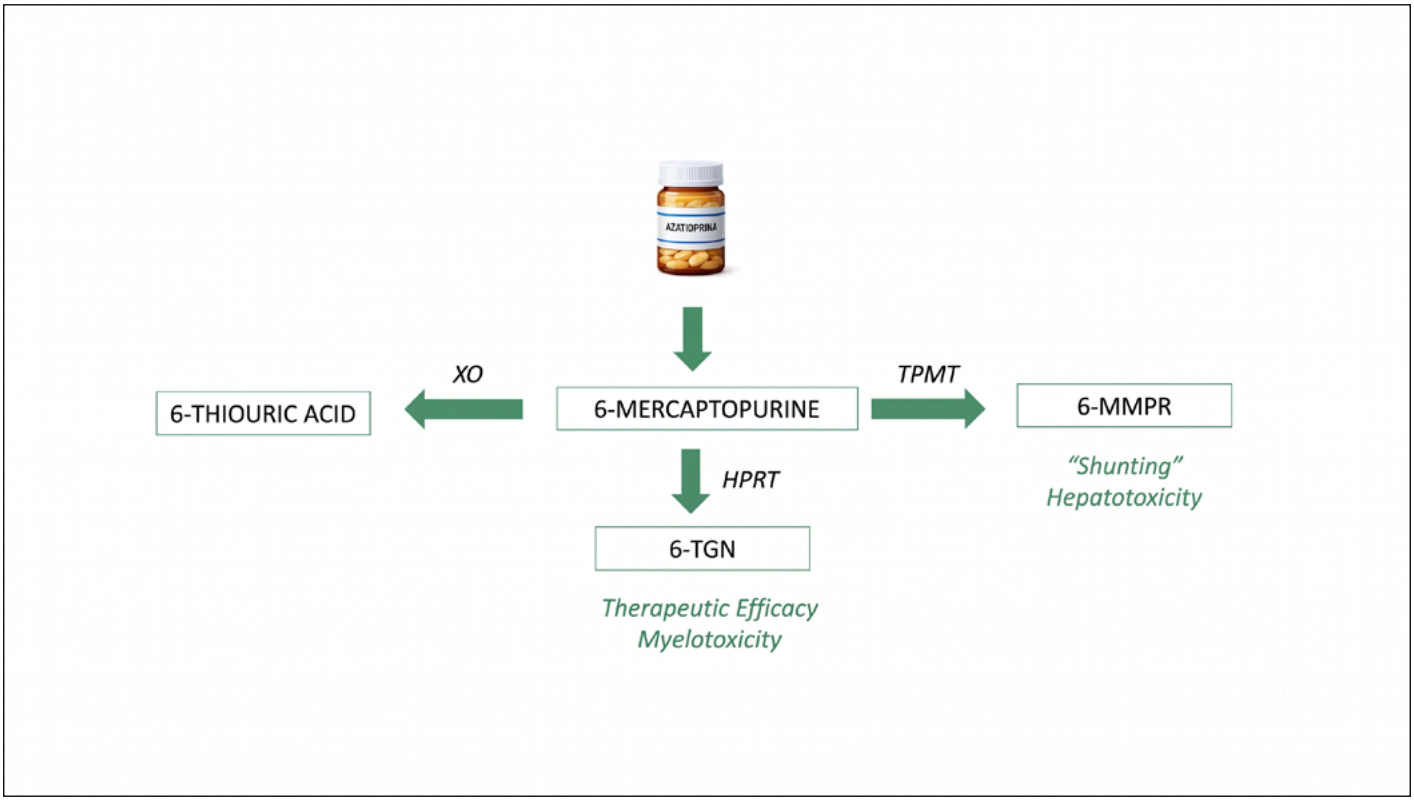

Figure 1. ***Thiopurine metabolism.***

always analyze 6-methylmercaptopurine (6-MMP) levels, as some patients preferentially metabolize 6-mercaptopurine (6-MP) into 6-MMP rather than 6-TGN, which poses a risk of hepatotoxicity without clinical benefit (these are known as "shunters"). In patients with low 6-TGN levels but high 6-MMP levels, the solution is not to increase the AZA dose, as this will increase hepatic toxicity. In these cases, 100 mg of allopurinol daily can be added, which will block xanthine oxidase and allow the AZA dose to be reduced to 25% of the original amount, shifting metabolism preferentially toward 6-TGN[5,10,12]. Figure 2 summarizes an algorithm for managing treatment failure.

Intolerance to standard therapy

The management of intolerance to standard treatment in AIH is a fundamental pillar of clinical practice, as general treatment intolerance occurs in 30.4% of patients within the first 6 months of treatment[14]. The following outlines a comprehensive approach to managing intolerance based on the drug involved:

1. Management of AZA intolerance. Intolerance to thiopurines is common and necessitates a change in treatment within the first 6 months in 36.5% of patients[14]. The most common side effects are nausea, vomiting, and abdominal pain (gastrointestinal symptoms), followed by fever, myalgia, and general malaise, which usually appear within the first two weeks of use; myelosuppression, pancreatitis, and hepatotoxicity are less frequent (<2%) but severe[5]. One option is to switch to 6-mercaptopurine (6-MP), since in some patients intolerance occurs due to a reaction to the imidazole component of AZA. It is estimated that between 50% and 75% of patients intolerant to AZA can tolerate 6-MP[1,15]. Additionally, we can monitor metabolites just as we do with AZA. Another option is to use MMF, a second-line drug that we will discuss below.

2. Management of corticosteroid intolerance. Between 25% and 70% of patients report side effects related to long-term steroid use, which significantly impacts their quality of life[5,8]. In patients without cirrhosis or portosystemic collaterals, budesonide is an alternative with high first-pass hepatic metabolism (90%), which significantly reduces systemic effects (Cushing's syndrome, acne, weight gain)[2,8,10]. However, it may be less effective than prednisone in cases of high inflammatory activity[10,11]. If intolerance is severe (uncontrolled diabetes, severe osteoporosis with fractures, psychosis), the steroid dose should be tapered rapidly under strict biochemical monitoring until monotherapy with AZA or MMF is achieved[12]. Finally, in specific populations where steroids are

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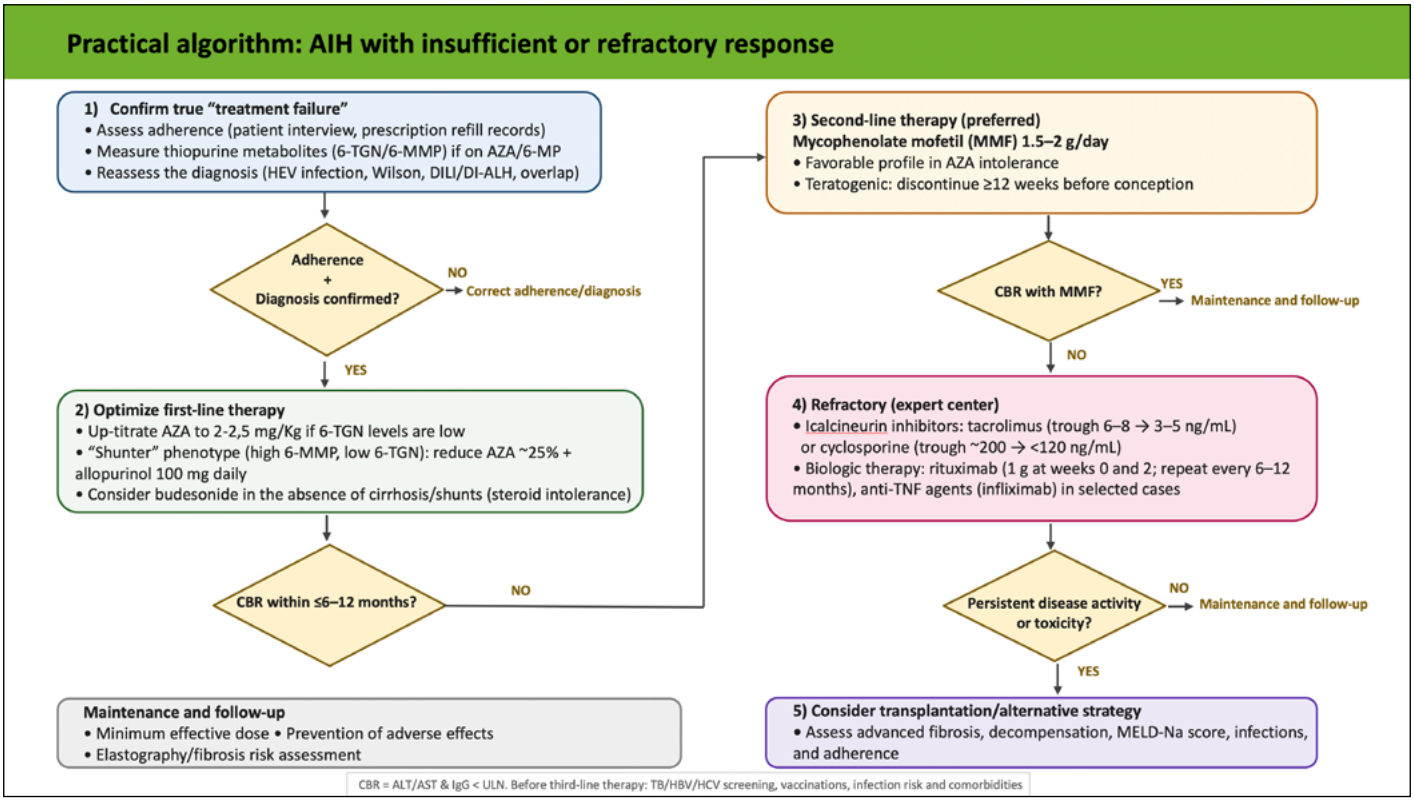

Figure 2. ***Practical algorithm insufficient or refractory response.***

undesirable (morbid obesity, severe metabolic syndrome, adolescents at risk of poor adherence due to body image concerns), rituximab has been used as an initial alternative to induce remission while avoiding exposure to corticosteroids[2].

Second- and third-line therapies

These are reserved for patients with an inadequate response to or proven intolerance of AZA. Table 2 summarizes the most commonly used agents.

1. Mycophenolate mofetil (MMF): This is the drug of choice for AZA intolerance, with response rates ranging from 62% to 92%[1,16]. However, its efficacy in patients with true non-response to AZA is significantly lower, achieving CBR in only 32% to 38% of cases, with factors independently associated with a poorer response including younger age, higher pretreatment IgG levels, and a longer duration of INR[6,17]. It is generally used at a dose of 1.5–2 g/day (divided into two doses), and it is crucial to remember that it is teratogenic, so it must be discontinued at least 12 weeks before conception.

   Recently, the use of MMF has established itself as an effective and safe alternative to standard first-line treatment[1,5]. This recommendation is primarily based on the results of the *CAMARO* clinical trial, which demonstrated the superiority of MMF over AZA in inducing CBR (72.2% vs. 32.3%)[18]. It also has significantly lower rates of serious adverse events and treatment discontinuation due to intolerance compared with AZA (5.1% vs. 25.8% in the CAMARO study)[18]. Although MMF is better tolerated, some experts still prefer AZA in certain contexts because its levels (6-TGN metabolites) can be monitored to optimize the dose, it is safe during pregnancy, and it is generally less expensive in many countries[11].

2. Calcineurin inhibitors. These are options typically used when both first- and second-line treatments fail. Their use is recommended in specialized centers[1,10]. By inhibiting calcineurin, an enzyme necessary to activate the nuclear factor of activated T cells, they prevent the synthesis of cytokines required for the development and survival of activated T cells[2].

   a. Tacrolimus (TAC): This is the best-studied third-line agent[1,12], although the available evidence is limited, based primarily on small, heterogeneous cohorts or case series without control groups[1,5]. The overall response rate is 74.7% in patients refractory to or intolerant of standard therapy[2,19]. Response rates in patients with an inadequate response range from 56% to 78%[20,21]. The usual dose is 0.1 mg/kg every 12

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Drug	Usual Line of Therapy	Suggested Dose	Preferred Clinical Context	Risks/Precautions
Mycophenolate mofetil (MMF)	2nd line	1.5–2 g/day (in 2 divided doses)	Azathioprine intolerance; selected alternative for induction therapy	Teratogenic; discontinue ≥12 weeks before conception; cytopenias/ infections
Tacrolimus	3rd line	0.1 mg/kg every 12 h (target trough level 6–8 ng/mL; maintenance 3–5 ng/mL)	Refractory disease or failure of 2nd-line therapy	Nephrotoxicity, hypertension, diabetes mellitus, neurotoxicity; monitor drug levels
Cyclosporine A	3rd line	2 mg/kg every 12 h (target level ~200 ng/mL; maintenance <120 ng/mL)	Alternative option; more commonly used in pediatric patients	Nephrotoxicity, hypertension, hypertrichosis, gingival hyperplasia
Rituximab	3rd line / rescue therapy	1 g IV at weeks 0 and 2; repeat every 6–12 months	Refractory disease; need for steroid sparing; poor treatment adherence	Infections; hypogammaglobulinemia; monitor IgG/IgM levels
Infliximab	Rescue therapy	5 mg/kg at weeks 0, 2, and 6; then every 8 weeks	Multidrug-resistant disease (expert centers)	High risk of infection; may induce de novo DI-ALH/AIH

Table 2. ***Second- and Third-Line Therapies: Indications, Suggested Doses, and Risks.***

hours to achieve trough levels of 6–8 ng/mL. Once a response is achieved, the dose should be gradually reduced to maintenance levels of 3–5 ng/mL[12]. TAC is a potent immunosuppressant with a narrow therapeutic window, so it requires close monitoring to track and manage potential and common adverse effects: nephrotoxicity, hypertension, hyperlipidemia, diabetes, etc.[1,5].

b. Cyclosporine A (CsA): As with TAC, the evidence is limited and based on experience from expert centers[2]. Experience with its use comes primarily from its use in the pediatric population, especially in severe cases or to prevent steroid-related side effects[1]. In the adult population, recent studies report a response rate of 35.4% in patients unresponsive to prior treatments, rising to 60% when including those with intolerance[22]. CsA is effective in inducing remission, particularly in steroid-resistant cases, serving as an alternative to steroids to avoid their adverse effects, which could be beneficial in the presence of certain comorbidities, such as obesity and diabetes[2]. However, it is not ideal for maintenance therapy due to its long-term side effects. The usual dose in adults is 2 mg/kg twice daily to achieve levels of approximately 200 ng/mL, with the dose reduced once remission is achieved to trough levels of <120 ng/mL[12]. Renal function must be closely monitored due to the risk of nephrotoxicity, as well as hypertension, gingivitis, neurotoxicity, etc.[2].

3. Biological agents: These are drugs used as third-line rescue therapy; their use is recommended by the European Association for the Study of the Liver (EASL) and the IAIHG in specialized centers due to the lack of randomized controlled trials[5]. It is very important to rule out latent infections prior to treatment (such as tuberculosis) and ensure a complete vaccination schedule[5,12]. It is also advisable to register cases in international networks, such as the European Reference Network for Rare Liver Diseases (ERN RARE-LIVER), to thereby strengthen the international scientific evidence regarding these therapies[12]. The use of the main agents is detailed below:

a. Rituximab. It is a chimeric monoclonal antibody that depletes B cells by binding to the CD20 antigen, thereby reducing antigen presentation to T cells, decreasing cytokine-mediated inflammation, and inhibiting the recruitment of effector cells to the liver[7]. Regarding its efficacy, in an international cohort of 22 treatment-resistant patients, biochemical improvement was observed in all cases, and 71% of patients remained flare-free at two years[23]. In a recent study from the Spanish ColHai registry, the response rate in refractory AIH was 86%, and it also allowed for a significant reduction in steroid dosage[24]. The usual dosage is 1 gram intravenously in weeks 0 and 2, with the dose repeated every 6–12 months depending on the biochemical response and B-cell repopulation[1]. Regarding safety, it is considered a drug with infrequent serious adverse effects, although there is a risk of serious infections, especially if severe hypogammaglobulinemia develops; therefore, monitoring of serum immunoglobulins, particularly IgG and IgM, is recommended before and during treatment[7].

b. Infliximab. It is a recombinant chimeric monoclonal antibody that blocks the binding of tumor necrosis factor alpha (TNF-α) to its receptors, inhibits the

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signaling pathways of proinflammatory cascades, and promotes apoptosis of activated T cells that produce TNF-α. In this way, it reduces disease activity in various autoimmune diseases[3,7]. In a multicenter retrospective study of 42 patients with AIH, infliximab induced or maintained complete biochemical remission in 78% of cases and specifically rescued 55–57% of patients who had failed previous second- or third-line treatments[3]. It is typically administered at a dose of 5 mg/kg at weeks 0, 2, and 6, and then every 8 weeks. It is considered a "double-edged sword" because, although it is effective as a rescue therapy, it can also induce immune-mediated liver injury that mimics or triggers *de novo* AIH[25,26]. It should also be noted that it has a high rate of infectious complications, reported in up to 64% of patients in some small series, particularly in those with underlying cirrhosis[1,27].

c. B-cell activating factor (BAFF) inhibitors. This is a cytokine belonging to the TNF family expressed by T and dendritic cells that plays a role in the development and differentiation of B cells. BAFF levels are associated with liver inflammation, so its inhibition could be a pathogenetically justified third-line treatment option[1,28].

i. Belimumab. This is a human antibody that inhibits soluble BAFF. It has been used empirically in refractory cases with encouraging results, achieving complete remission and improvement in fibrosis in some case reports[29].

ii. Ianalumab (VAY736). Targeting the BAFF receptor (BAFF-R), it promotes B-cell elimination through antibody-dependent cellular cytotoxicity[8]. It is currently being evaluated in a Phase II/III clinical trial (NCT03217422) for refractory or intolerant patients[7].

d. Other agents.

i. Basiliximab. An anti-CD25 (IL-2 receptor) antibody that inhibits T-cell activation. Its successful use has been reported in isolated cases of severe AIH associated with immune checkpoint inhibitors[9].

ii. Tocilizumab (anti-IL-6). It is considered a potential option given the importance of IL-6 in Th17 cell differentiation in AIH[8].

iii. JAK Inhibitors (Tofacitinib). It has been used as a rescue therapy in patients who do not respond to previous biologics, showing improvement in transaminase levels[3].

Management of Acute and Severe Autoimmune Hepatitis

The therapeutic approach for patients with acute and/or severe presentations of AIH is a complex situation that requires rapid decision-making and often the intervention of a liver transplant center, as the prognosis without treatment is very poor [5,10].

As noted earlier, acute and severe presentations of AIH include Severe Acute AIH, acute liver failure, and acute-on-chronic liver failure. The primary goal is to rapidly initiate a therapeutic trial with corticosteroids to induce remission and avoid the need for liver transplantation, or to refer the patient directly to a transplant center if the prognosis is extremely poor[5,6].

1. Induction therapy with corticosteroids. Initial treatment for AIH, ALF, or ACLF is intensive and based on corticosteroids. In adults, early treatment with prednisolone at 0.5–1 mg/kg/day or intravenous (IV) methylprednisolone at an equivalent dose is recommended[5,11]. In children, prednisolone at 2 mg/kg/day or an equivalent IV dose (IV methylprednisolone doses equivalent to 0.5–1 mg/kg/day have been used)[6,10].

Combination with AZA is contraindicated as it could cause toxicity and make it difficult to distinguish between lack of response and AZA-induced hepatotoxicity. Budesonide is also contraindicated in patients with a severe acute course of the disease or with established cirrhosis, as its first-pass metabolism is impaired in these cases, increasing toxicity[5,6].

2. Rapid assessment of response and criteria for LT. Response to treatment must be evaluated very closely and rapidly, with laboratory tests performed every 12–24 hours[6]. Management of acute and severe forms requires strict monitoring due to the risk of rapid deterioration; it is crucial to assess the response to corticosteroids or determine whether the patient should be urgently referred for LT[5,11].

In severe cases without ALF or ACLF, the benefit of early corticosteroid therapy is highly significant, with transplant-free survival rates ranging from 52% to 95.2%[5].

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Predictive models have been developed to assess lack of response to corticosteroids and the need for LT, such as the SURFASA score, which evaluates the INR at the start of steroid therapy and its change, as well as bilirubin levels on the third day of treatment[30] or a nomogram based on age, the MELD (Model for End-Stage Liver Disease) score, hepatic encephalopathy, and ascites, with the MELD score on the 7th day of steroid treatment being the best univariate predictor of response[31].

In cases of ALF and ACLF, patients have the worst prognosis, with steroid response rates ranging from 8% to 41%; therefore, immediate consultation with a LT centre is recommended, as data on the role of steroids in these patients are limited and outcomes are generally poor[5]. If corticosteroids are administered, close monitoring for possible infections is necessary, as the risk of infection is increased[5] (Figure 3).

Management of overlap syndromes

The management of overlap syndromes (or variants) involving AIH requires an approach based on the predominant component of the disease, given that these patients exhibit clinical, serological, and histological features of both AIH and an autoimmune cholestatic disease, primarily PBC or PSC.

The following details the approach for the two main overlap syndromes:

1. AIH/PBC overlap syndrome. It affects nearly 10% of adults with AIH or PBC[6,8]. The diagnosis is established using the Paris criteria, which are the most validated for this syndrome and encompass diagnostic features of both conditions (Table 1)[6]. The initial treatment regimen should be determined based on biochemical parameters and histological findings[5]:

a. If AIH is the predominant component (i.e., moderate or severe hepatitis based on the modified histological activity index score—mAIH): standard immunosuppressive therapy (corticosteroids with or without AZA) followed by the addition of ursodeoxycholic acid (UDCA) at a dose of 13–15 mg/kg/day if there is no response. The latest EASL guidelines suggest combining both from the outset to protect against long-term complications of PBC (such as the development of ductopenia and biliary-related cirrhosis)[5].

b. If the cholestatic component is predominant (i.e., only mild hepatitis on biopsy), monotherapy with UDCA may be used initially, and immunosuppressive

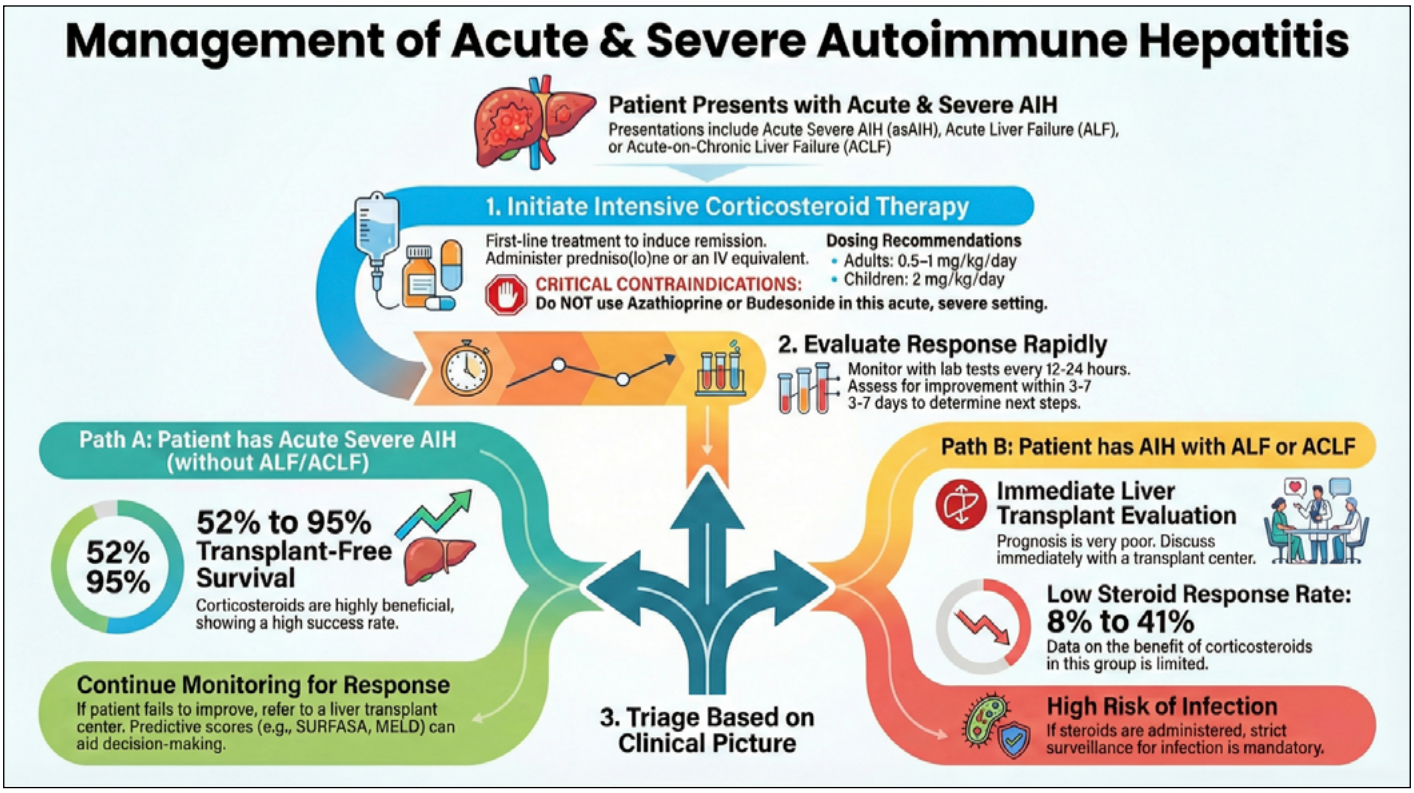

Figure 3. ***Management of acute and severe AIH.***

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agents may be added if the patient does not achieve CBR.

2. AIH/PSC overlap syndrome. This syndrome is reported primarily in children, adolescents, and young adults[8]. In the pediatric population, it may be referred to as autoimmune sclerosing cholangitis (ASCC), which can be considered part of the spectrum of the variant form of PSC with a strong inflammatory component[5]. For diagnosis, magnetic resonance cholangiography (MRCP) is recommended for the initial evaluation of all cases of AIH in childhood, regardless of whether cholestatic enzymes are elevated, as well as in young adults with cholestasis or those who do not achieve CBR[5,6]. If disease activity persists or cholestatic features are present at follow-up, MRCP should be repeated. Other features suggesting underlying PSC in patients with AIH include prominent splenomegaly, marked portal hypertension, and evidence of concomitant inflammatory bowel disease[5]. Treatment of this variant is also determined based on the predominant component:

a. If the simplified AIH score is >5 and the mAIH is >3, a combination of immunosuppressive therapy and UDCA (13–15 mg/kg/day) is recommended. The beneficial role of immunosuppression has been confirmed in these cases.

b. If these AIH criteria are not met, then use UDCA at doses of 13–23 mg/kg/day.

In cases with additional PSC criteria, the need for endoscopic intervention to treat high-grade strictures should be evaluated[10].

Patients with AIH/PSC generally have a worse prognosis than patients with AIH alone or AIH/PBC, as liver fibrosis may progress even with combination therapy[5].

Management of autoimmune hepatitis during pregnancy.

The management of AIH during pregnancy is a critical issue that requires a coordinated multidisciplinary approach between hepatologists and obstetricians. In general, pregnancy is viable and safe for most patients with AIH, especially if the disease is well controlled prior to conception[5,10]. AIH is associated with a slight decrease in fertility, particularly in cases of cirrhosis or poorly controlled disease, but most patients can conceive successfully[6]. It is essential to discuss plans for childbearing before initiating certain treatments. It is recommended that the patient remain on CBR for at least 24 months before attempting to conceive, as this reduces the risk of flare-ups and preterm birth[32]. Here are some key points:

1. Fetal and maternal risks. Patients with AIH have a higher risk of complications compared to the general population[6].

a. Maternal complications: Higher likelihood of gestational diabetes (OR 2.84) and hypertensive complications such as preeclampsia, eclampsia, and HELLP syndrome (OR 2.22)[33]. The overall rate of maternal complications is 38% during pregnancy or the first postpartum year, and the highest risk occurs when cirrhosis is established[6].

Characteristic	AIH	DI-ALH
Temporal relationship with drug exposure	Not required	Typical (previous 3–12 months)
Course after drug withdrawal	Not applicable	Improvement expected
Relapse after corticosteroid withdrawal	Frequent	Uncommon if true DI-ALH
Advanced fibrosis/cirrhosis	May be present	Less frequent
Need for long-term IS	Common	No (if DI-ALH)

Notes: DI-ALH: drug-induced autoimmune-like hepatitis.

Table 3. ***DI-ALH: drug-induced hepatitis with an autoimmune phenotype.***

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b. Fetal outcomes: There is an increased risk of preterm birth, low birth weight, and small-for-gestational-age infants. The rate of fetal loss and intrauterine fetal death is approximately 27%[6]. The presence of portal hypertension is associated with a higher frequency of preterm births[5].

2. Pharmacological management. Adjusting medication is the key to safe management:

a. Safe medications (continue): Maintenance therapy with thiopurines, with or without corticosteroids, should be continued throughout pregnancy. These drugs are not associated with an increased risk of fetal complications and are also safe during breastfeeding[5].

b. Contraindicated medications (discontinue): MMF is highly teratogenic. It must be discontinued at least 3 months (12 weeks) prior to conception in both women and men (due to the risk of genotoxicity)[5]. The use of allopurinol is also contraindicated during pregnancy due to its teratogenic risk.

3. New diagnoses: If AIH presents for the first time during pregnancy, standard steroid-based regimens should be used, strictly excluding MMF.

4. Risk of flares. The course of AIH varies significantly by trimester. During pregnancy, flares are relatively rare (13%), as hormonal and immunological changes typically provide good disease control, especially in the first and second trimesters[10]. The postpartum period is the time of greatest risk. It is estimated that 41% of patients experience a flare-up (typically around 11 weeks postpartum). This requires close monitoring and, often, preventive intensification of immunosuppression after delivery[5].

Management of Drug-Induced Autoimmune-Like Hepatitis (DI-ALH)

The therapeutic approach to DI-ALH differs from that of classic AIH, as DI-ALH is a transient condition that, in most cases, resolves after discontinuation of the causative agent[5,10]. The key to management lies in the immediate withdrawal of the suspected drug and close monitoring to differentiate it from idiopathic AIH, which requires long-term immunosuppression. The recommended therapeutic approach for DI-ALH, according to the latest EASL guidelines[5](Table 3), is detailed below:

1. Immediate withdrawal of the causative agent. This is the initial and most important step (drugs, herbs, dietary supplements, or vaccines). DI-ALH has been associated with more than 40 different substances, including minocycline, nitrofurantoin, hydralazine, methyldopa, imatinib, statins, and biologics such as infliximab or adalimumab[4]. Exposure generally must have occurred within 3 to 12 months prior to the onset of hepatitis[5].

2. Corticosteroid treatment. In many cases, the disease resolves spontaneously after the causative agent is removed. However, corticosteroid therapy is indicated in specific situations:

a. A short course of prednisolone is recommended in patients with severe hepatitis, impaired liver function, or those who do not show improvement in liver function tests within 30 days after discontinuation of the implicated agent. Patients with severe DI-ALH who meet the Hy criteria (ALT >3 times ULN and total bilirubin >2 times ULN) and who have not achieved biochemical resolution by 30 days benefit from corticosteroid treatment. The recommended regimen is an initial dose of 0.5 mg/kg/day, followed by rapid and progressive tapering until complete withdrawal, generally within 1 to 2 months. Liver biopsy is considered highly useful before initiating corticosteroids to confirm AIH-like lesions histologically and rule out other conditions.

3. Differential diagnosis based on the course of the disease. The prognosis and the need for long-term treatment are the most important distinguishing factors between DI-ALH and classic AIH. If hepatitis resolves without relapse after corticosteroid withdrawal, a diagnosis of DI-ALH is assumed. Otherwise, the diagnosis of AIH is confirmed, and standard combined induction and maintenance therapy (corticosteroids with AZA or MMF) should be initiated. The histological features of DI-ALH may be indistinguishable from those of AIH, as it may present with lymphoplasmacytic infiltrate and interface hepatitis. However, the finding of advanced fibrosis/cirrhosis is less common in DI-ALH[6].

Management of patients with AIH and decompensated cirrhosis

The management of patients with AIH and decompensated cirrhosis is a highly complex and high-risk situation that requires rapid and coordinated care, prioritizing

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evaluation for liver transplantation; therefore, management should be conducted at referral centers or in consultation with experts, due to the high risk of complications and the limited evidence available regarding treatment in this subgroup[5]. One of the main and most controversial issues is the decision to initiate immunosuppressive therapy due to the risk of complications, particularly infectious ones (the leading cause of mortality); consequently, there is little published data on this topic[34,35]. In general, its use is considered if there are signs of active AIH, that is, elevated aminotransferases and/or an mAIH >4. In these cases, prednisolone is used at a dose of 20–30 mg daily[5], always under strict monitoring for possible infections. A recent study shows that the main predictors of response are hepatic encephalopathy and the MELD-Na score (sodium-adjusted Model for End-Stage Liver Disease) and serve to guide the therapeutic decision[36]. Patients with grade 3 or 4 encephalopathy have a 7% probability of transplant-free survival (TFS) if they initiate immunosuppressive therapy; therefore, in this situation, they should always be considered for early initiation of LT. Patients with grade ≤ 2 encephalopathy have a TFS of 60% with immunosuppressive therapy, but only 12% if the MELD-Na > 28 compared to 64% if it is ≤ 28. Thus, patients with grade ≤ 2 encephalopathy and MELD-Na > 28 will also be considered for immediate LT[36].

Management of AIH in patients with MASLD

The management of AIH in patients with MASLD requires a personalized and multidisciplinary approach due to the complexity of the coexistence of both conditions[5]. The prevalence of MASLD in patients with AIH is similar to that in the general population; therefore, the coexistence of these conditions is not uncommon and is associated with greater severity and a poorer prognosis[37]. The recommended approach is as follows:

1. Treatment principles and general approach. Patients should receive standard treatment for AIH with the goal of achieving complete remission and preventing the progression of liver disease without exacerbating MASLD.

2. Management of immunosuppression. The use of corticosteroids in this subpopulation should be cautious, as they can exacerbate hepatic steatosis, obesity, hypertension, and peripheral insulin resistance. A personalized and multidisciplinary approach is recommended for the administration of prednisolone, aiming for the lowest effective dose and planning for a more rapid tapering[5].

3. Management of MASLD. It is essential to control the components of metabolic syndrome (diabetes, hypertension, dyslipidemia, obesity, etc.) to improve prognosis and prevent complications; in many cases, a multidisciplinary approach involving other specialties is necessary, and lifestyle changes aimed at weight loss—including exercise, dietary modifications, and behavioral therapy—must also be implemented[5,6].

4. Treatment monitoring. The coexistence of MASLD can complicate the assessment of response to treatment for AIH, as the presence of steatosis may prevent complete normalization of liver function tests, which affects the definition of CBR. Patients with AIH and MASLD tend to have lower levels of aminotransferases, alkaline phosphatase (ALP), and IgG compared to those with AIH alone[11]. In cases of insufficient response to treatment, a follow-up liver biopsy may be necessary to differentiate the relative roles of AIH activity and MASLD in abnormal laboratory values[5,12].

Conclusions

The management of complex AIH requires a shift from rigid protocols toward personalized medicine. The judicious use of biomarkers (metabolites), the early use of therapeutic alternatives and dynamic prognostic algorithms, as well as new biologic therapies, is redefining the options for patients who do not respond to conventional treatment or who are in special situations or have comorbidities that cannot be ignored. Success depends on accurate diagnosis, strict monitoring of adherence, and multidisciplinary management in specialized centers.

Statement on the Use of Artificial Intelligence

The authors declare that an artificial intelligence tool (NotebookLM, Google) was used to assist in organizing the literature and generating preliminary drafts of some sections of the manuscript, using exclusively the articles selected by the authors. All content was critically reviewed, corrected, and validated by the authors, who assume full responsibility for the accuracy, integrity, and originality of the work. This use does not imply that IA performed independent scientific interpretation or analysis of non-bibliographic data.

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CLINICAL CASE

HEPATOCELLULAR CARCINOMA IN A PATIENT WITH ACUTE INTERMITTENT PORPHYRIA: IMPORTANCE OF DIGESTIVE FOLLOW-UP.

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Abstract

Acute intermittent porphyria (AIP) is a rare metabolic disorder with autosomal dominant inheritance and low penetrance that may be associated with severe long-term hepatic complications, including hepatocellular carcinoma (HCC), even in the absence of liver cirrhosis. We present the case of a 76-year-old woman with a previous diagnosis of AIP and stage IV chronic kidney disease, without regular follow-up by the gastroenterology department. During an abdominal ultrasound performed as part of her nephrological follow-up, a large hepatic mass was incidentally detected. Further evaluation with computed tomography and contrast-enhanced magnetic resonance imaging revealed an 8-cm lesion in segment VII with imaging features consistent with hepatocellular carcinoma (LI-RADS 5), arising in a non-cirrhotic liver. Histological confirmation was obtained after biopsy, which was complicated by a perihepatic hematoma. Due to age and comorbidities, curative treatments were ruled out; transarterial chemoembolization (TACE) and transarterial radioembolization (TARE) were also considered non-curative locoregional options in this setting, and systemic therapy with sorafenib was initiated. Patients with AIP have an increased risk of developing HCC, regardless of the presence of cirrhosis, particularly after the age of 50. Lack of structured digestive and hepatological follow-up may delay diagnosis and limit therapeutic options. Regular follow-up by gastroenterology and hepatology, including periodic liver imaging, is essential in patients with AIP to enable early detection of hepatocellular carcinoma and improve clinical outcomes.

Keywords: acute intermittent porphyria, hepatocellular carcinoma, follow-up, non-cirrhotic liver.

Introduction

Porphyrias are a heterogeneous group of rare metabolic disorders—either hereditary or acquired—caused by abnormalities in the activity of enzymes involved in heme biosynthesis, leading to the accumulation of toxic precursors with systemic effects[1]. Depending on the location of the enzymatic defect, they are classified as hepatic or

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erythropoietic porphyrias, and depending on their clinical presentation, as acute or cutaneous forms.

Acute intermittent porphyria (AIP) is the most common form of hereditary acute porphyrias. It is caused by a deficiency of the enzyme porphobilinogen deaminase, leading to the accumulation of delta-aminolevulinic acid (ALA) and porphobilinogen (PBG), both of which have neurotoxic effects[1,2]. It is inherited in an autosomal dominant pattern with low penetrance, meaning that most carriers remain asymptomatic until exposed to triggering factors such as certain medications, prolonged fasting, alcohol consumption, infections, physical or emotional stress, and hormonal changes[1].

Clinically, AIP episodes present with severe abdominal pain, peripheral and autonomic neurological symptoms, psychiatric disturbances, and fluid and electrolyte imbalances, making it a significant cause of recurrent abdominal pain of unknown origin. Beyond acute episodes, AIP is associated with chronic complications, notably hypertension, chronic kidney disease, and the development of progressive liver disease, including cirrhosis and hepatocellular carcinoma[1,3].

Several studies have demonstrated an increased risk of HCC in patients with AIP, even in the absence of liver cirrhosis, underscoring the importance of regular hepatological follow-up in these patients.

We present an illustrative case of this complication in a patient with no known chronic liver disease.

Clinical case

A 76-year-old woman, partially dependent for activities of daily living, with a family history of acute intermittent porphyria (affected sister). Her personal medical history included AIP diagnosed years earlier, with previous episodes of recurrent abdominal pain treated symptomatically, and stage IV chronic kidney disease being monitored by the nephrology department.

The patient was not undergoing regular follow-up for gastrointestinal or hepatological conditions, despite her diagnosis of AIP. In the preceding months, she had visited the emergency department on several occasions for nonspecific abdominal pain, with no conclusive findings on the tests performed.

During an abdominal ultrasound ordered as part of her nephrology follow-up, a large solid hepatic mass was incidentally detected. The workup was completed with an abdominal CT scan and contrast-enhanced liver MRI, which revealed a lesion measuring approximately 8 cm located in segment VII, hypervascular in the arterial phase with washout in the late phases, consistent with hepatocellular carcinoma (LI-RADS 5), in a liver of normal size, contour, and parenchyma.

The case was presented to a multidisciplinary liver tumor committee. Given the partially atypical radiological appearance of the lesion and the absence of cirrhosis or known chronic liver disease, it was decided to perform a liver biopsy for diagnostic confirmation. The procedure, performed by the vascular radiology team, was complicated by the development of a perihepatic hematoma with active extravasation, which required a transfusion of packed red blood cells and subsequent conservative management.

The histopathological examination confirmed the diagnosis of hepatocellular carcinoma. Following a committee review and considering the patient's age, functional status, and associated comorbidities, curative treatment options such as resection or liver transplantation were ruled out. Likewise, TACE and TARE were considered non-curative locoregional alternatives that were not appropriate in this case; therefore, systemic treatment with sorafenib was initiated.

Discussion

AIP is a rare condition with autosomal dominant inheritance and low penetrance, caused by a deficiency of porphobilinogen deaminase. Although it has traditionally been recognized for its acute neurovisceral crises, it is now known to be a multisystemic disease with significant chronic complications, including hypertension, chronic kidney disease, and liver neoplasms[1,2]. This longitudinal perspective is important, as some patients may present with minimal acute clinical activity yet remain at risk for long-term complications.

From an epidemiological standpoint, the accumulated evidence shows a clear increase in the risk of hepatocellular carcinoma in acute hepatic porphyrias, especially in AIP. In a Swedish cohort of 1,244 patients with acute hepatic porphyria, the risk of primary liver cancer was significantly higher than in the general population, and in patients over 50 years of age with a history of biochemical activity, the annual incidence reached 1.8%[3]. Consistent with this, U.S. studies and a recent meta-analysis confirm that HCC can occur in the absence of cirrhosis and that the risk increases with age, particularly after age 50[4,5].

This behavior distinguishes HCC associated with AIP from that observed in most cases of hepatocellular carcinoma in

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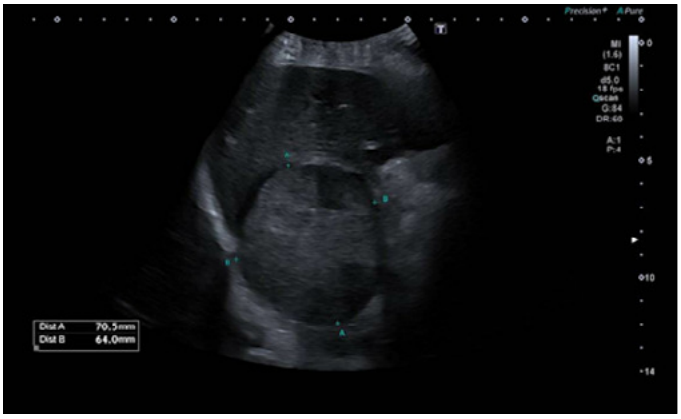

Figure 1. ***Liver of normal size, contour, and echogenicity. A solid mass measuring approximately 8 × 6 cm is identified in the right hepatic lobe, located in segment VII, extending beyond the liver margin.***

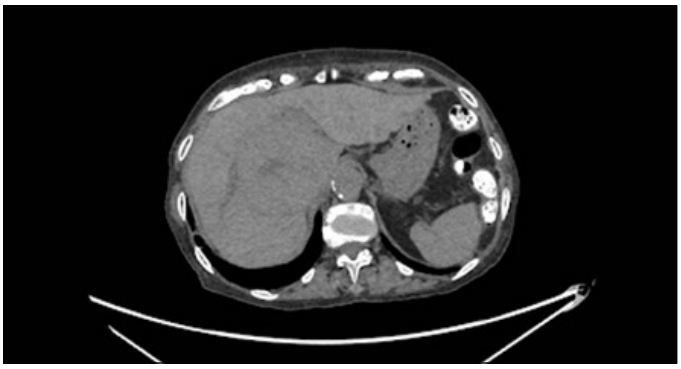

Figure 2. ***Liver of normal size and attenuation. A large, well-defined hepatic mass with central scarring is observed in segment VII, measuring approximately 7.5 × 8 × 7.7 cm.***

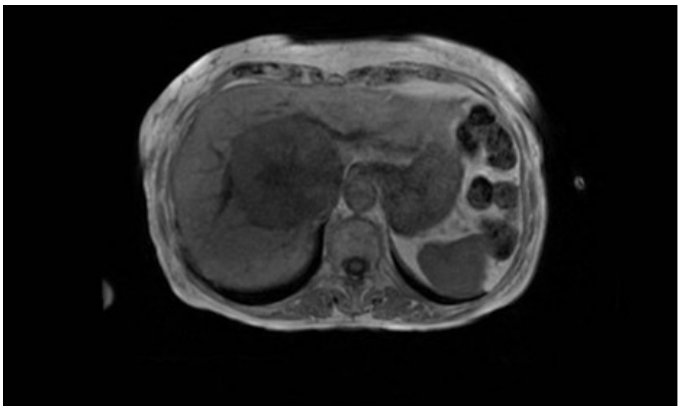

Figure 3. ***A hepatic mass measuring approximately 8 cm with features consistent with hepatocellular carcinoma (LI-RADS 5) on a non-cirrhotic liver; the mass is hypervascular in the arterial phase with washout in the late phases.***

the general population, which are typically linked to advanced chronic liver disease or cirrhosis. Therefore, conventional screening programs based exclusively on cirrhosis may fail to identify these at-risk patients. Consequently, various authors and reference documents recommend periodic liver monitoring in patients with acute hepatic porphyria starting at age 50, generally through annual ultrasound, with or without alpha-fetoprotein testing according to local protocols[1-5].

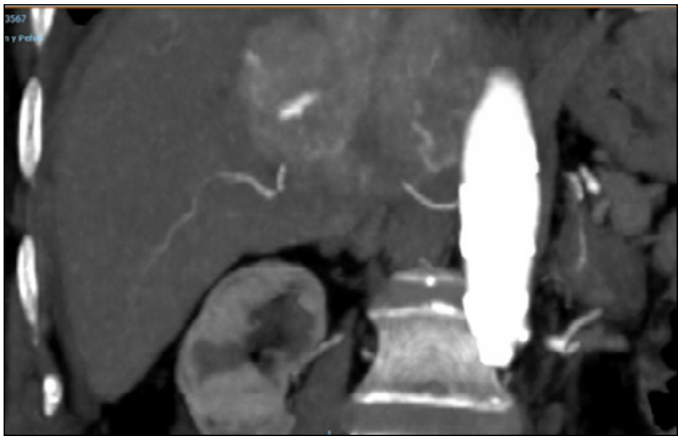

Figure 4. ***A perihepatic hematoma is evident with a focus of active extravasation in the arterial phase, consistent with a post-biopsy complication.***

The case presented here highlights how a lack of gastrointestinal follow-up can delay the diagnosis of a serious complication and limit available treatment options. The incidental detection of the tumor during an ultrasound examination ordered for another reason underscores the need for structured, protocol-based surveillance in patients with AIP. When the diagnosis is made at advanced stages or in elderly patients with comorbidities, potentially curative options may not be feasible; furthermore, locoregional treatments such as TACE or TARE, although useful in selected scenarios, should not be considered curative treatments in and of themselves.

With regard to the specific treatment of porphyria, the development of givosiran has represented a significant advance for patients with acute hepatic porphyria and recurrent attacks, as it has led to a sustained reduction in the annualized attack rate, the use of hemin, and the burden of symptoms[6]. However, its primary role is to control the underlying disease, and it does not replace liver monitoring, as the risk of liver cancer persists as a long-term complication that requires specific follow-up. In selected patients with severe AIP, liver transplantation may also correct the underlying metabolic defect, although its indication must be determined on a case-by-case basis according to age, comorbidities, and oncological status[1,2].

From a practical standpoint, this case reinforces the need to establish specific follow-up programs for patients with AIP, coordinated among primary care, gastroenterology/hepatology, and other relevant specialties. Such programs should include education on precipitating factors, monitoring of chronic complications, and periodic liver imaging starting at age 50, even in the absence of cirrhosis or abnormal liver function tests. Early identification of liver lesions can broaden therapeutic options and decisively influence the clinical course.

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CLINICAL CASE

PLUMMER-VINSON SYNDROME AS AN UNCOMMON CAUSE OF PROGRESSIVE DYSPHAGIA

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Abstract

Plummer–Vinson syndrome (PVS) is a very rare condition associated with iron-deficiency anemia and an increased risk of squamous cell carcinoma of the upper gastrointestinal tract.

We present the case of a 65-year-old woman with progressive dysphagia in whom endoscopic evaluation revealed cervical esophageal webs. Treatment with endoscopic dilation and iron supplementation led to clinical resolution.

This case highlights the importance of considering PVS in the differential diagnosis of dysphagia and of implementing targeted management with appropriate follow-up.

Keywords: Plummer-Vinson, esophageal web, dysphagia, anemia.

Introduction

Plummer-Vinson syndrome is a very rare clinical condition defined by the triad of iron-deficiency anemia, dysphagia, and esophageal membranes, and its presentation has been described predominantly in middle-aged women[1]. Its pathophysiology is not fully understood, although it has been proposed that iron deficiency promotes epithelial atrophy and impairments in mucosal repair[2].

Clinical case

A 65-year-old woman was referred for progressive dysphagia with solids that had been present for 12 months, associated with weight loss. The symptoms were initially attributed to poorly fitting dentures and possible oral candidiasis, but there was no improvement following treatment.

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Physical examination revealed glossitis, angular cheilitis, and a depapillated tongue. Laboratory tests showed iron-deficiency anemia.

The esophagogram revealed a proximal esophageal membrane. Upper gastrointestinal endoscopy confirmed stenosis secondary to two cervical esophageal membranes without associated malignant lesions. Progressive endoscopic balloon dilation was performed (initially 7–8 mm, increased to 10–12 mm in a second session) without complications, resulting in immediate symptomatic improvement. Treatment with oral iron was initiated, and laboratory values subsequently returned to normal.

Discussion

PVS is currently a rare cause of dysphagia in developed countries[1]. Its diagnosis may be delayed because symptoms are initially attributed to more common causes. Recognition of mucocutaneous signs of iron deficiency can guide the diagnosis.

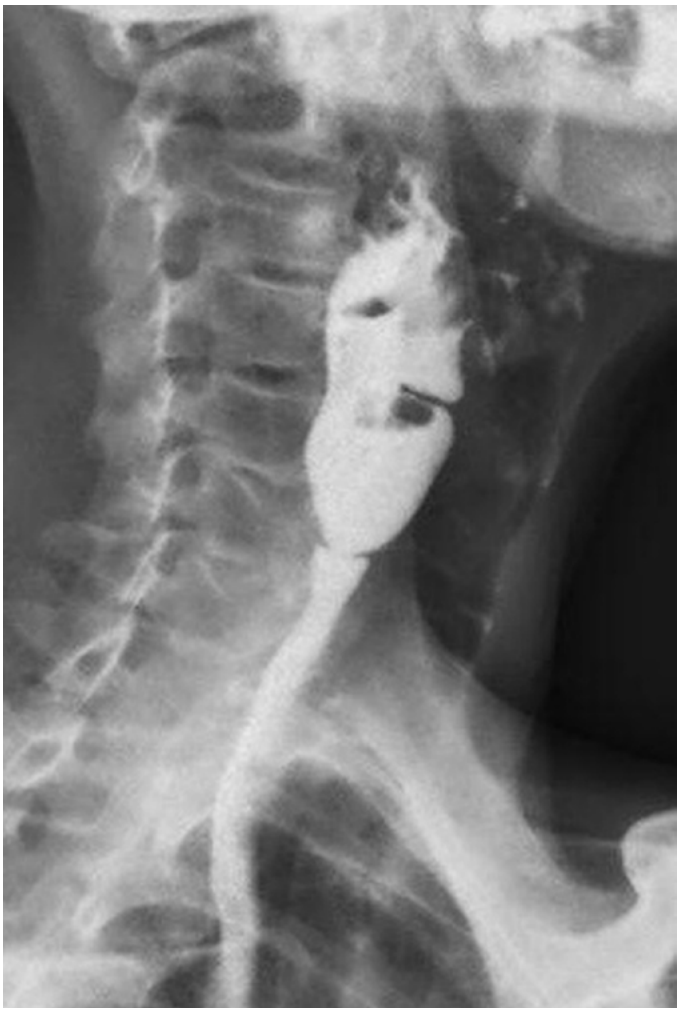

Figure 1. ***Barium esophagram showing a proximal esophageal membrane with concentric narrowing of the lumen, a characteristic finding of Plummer-Vinson syndrome.***

Iron supplementation forms the basis of treatment and can improve dysphagia in the early stages, whereas in cases with established stenosis, endoscopic dilation is safe and effective[1,2]. Despite its current low prevalence in developed countries, it remains clinically significant due to its association with squamous cell carcinoma of the hypopharynx and esophagus, underscoring the importance of early diagnosis and regular clinical follow-up[3].

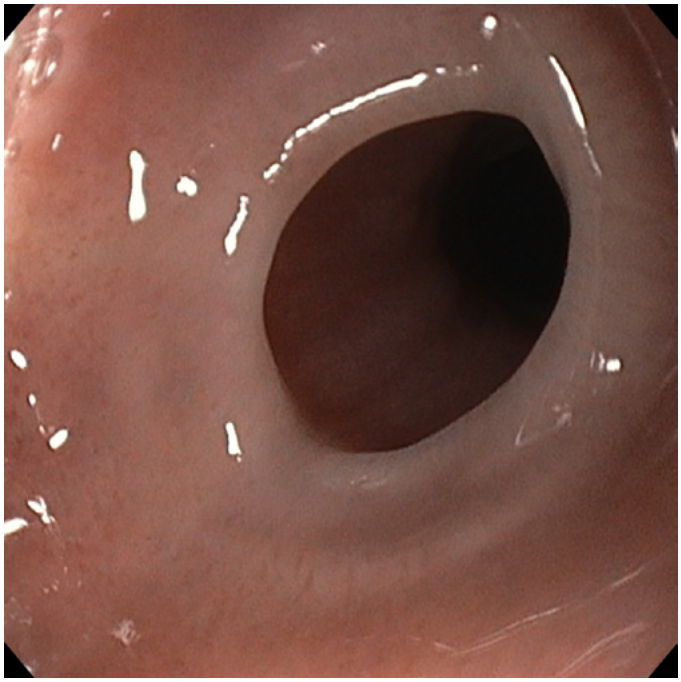

Figure 2. ***Upper gastrointestinal endoscopy showing a cervical esophageal membrane with concentric narrowing of the lumen and a reduced central orifice, consistent with Plummer-Vinson syndrome.***

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VIDEOFORUM

UTILITY OF THE MANTIS™ CLIP TO FACILITATE EXPOSURE AND RESECTION OF A LESION ON THE ILEOCECAL VALVE

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Abstract

The endoscopic resection of complex colorectal lesions presents a significant technical challenge, particularly for those located on the ileocecal valve, as this structure is mobile in some cases and may be difficult to access and to achieve stable exposure. Suboptimal exposure is a risk factor for incomplete resection and local recurrence. To overcome these difficulties, endoscopists rely on various techniques. We present the clinical case of a female patient with an adenomatous lesion on the ileocecal valve, whose challenging exposure was successfully resolved using the Mantis™ clip as a traction device. This adjustable and repositionable clip, primarily designed for tissue approximation and defect closure, proved to be an effective tool for optimizing lesion exposure, enabling a complete and precise endoscopic mucosal resection (EMR).

Keywords: endoscopic mucosal resection, ileocecal valve, mantis clip.

Introduction

Endoscopic Mucosal Resection (EMR) is the standard technique for managing superficial colorectal lesions. Most polyps detected during screening colonoscopies are small, benign, and easy to manage endoscopically. However, approximately 10–15% of colorectal polyps are classified as complex[1]. The term "complex" reflects the varying degrees of difficulty related to size, shape, extent, location, and the presence of scarring, which ultimately contribute to the complexity of resection using conventional endoscopic methods. Complex polyps are generally defined as lesions whose endoscopic resection is technically difficult. These include:

- Size: > 20 mm.
- Flat or depressed morphology.

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· Extent: polyps that occupy more than one-third of the circumference of the lumen, that encircle a fold (clam-shell polyps), or that span two haustral folds.

· Location: right colon, ileocecal valve, appendicular orifice, sigmoid colon, dentate line, and the inner curve of the hepatic and splenic flexures.

Resection of complex lesions poses a technical challenge. The ileocecal valve is considered one of the most difficult locations because it is a mobile structure that, in some cases, presents difficulties in terms of access and achieving stable exposure[2].

The clinical guidelines of the European Society of Gastrointestinal Endoscopy (ESGE) recommend that complex lesions and those located in hard-to-reach areas be managed at referral centers and, if necessary, using advanced resection and visualization techniques[3].

To counteract suboptimal exposure, accessories such as caps are used, or techniques such as submucosal injection with low-diffusion agents or mechanical traction (using thread clips or grasping forceps). The use of traction is essential in advanced therapeutic endoscopy, as it transforms the field of view, allowing for constant exposure of the tissue and better identification of the submucosal plane[4].

The Mantis™ clip is an adjustable, repositionable edge-gripping and approximation system designed for the approximation and closure of large mucosal defects[5,6]. Due to its anchoring characteristics and strong gripping capacity (TruGrip™ tips), it is considered an advanced traction tool in difficult exposure scenarios such as the one described below.

Clinical case

We present the case of a 68-year-old woman who underwent a screening colonoscopy due to a family history of colorectal cancer. During the examination, a flat, elevated lesion (0-IIa) was identified on the anterior leaflet of the ileocecal valve, extending and protruding into the ileum, with the lesion unable to be fully assessed. An attempt was made to expose the lesion using a cap and alligator forceps; however, these maneuvers provided only temporary exposure before the lesion retracted into the ileum, making it impossible to perform a stable assessment and plan the endoscopic mucosal resection (EMR) appropriately.

Given this limitation, the Mantis™ clip was used, which allowed the mucosa adjacent to the lesion to be secured to a distal haustra. This clip uses anchoring prongs to maintain a secure grip on the edges of the tissue. In the drag technique, the clip is opened and closed (without releasing it) at the proximal edge of the lesion. It is then gently guided toward the haustra, where it is opened again, closed at the opposite edge, and finally released. Through this controlled traction maneuver, the lesion was successfully brought to the surface in a continuous and stable manner.

The lesion was classified as NICE 2 and measured approximately 19 mm. With the aid of the cap and following elevation with saline, resection was performed using a hot snare, resulting in two fragments. Pathological examination confirmed a tubulovellous adenoma with high-grade dysplasia. The patient experienced no post-procedural complications and was scheduled for endoscopic follow-up to monitor the resection site.

Discussion

Therapeutic endoscopy of lesions at the ileocecal valve requires a high level of technical skill due to the risk of perforation and the challenge of achieving complete resection in an area of high mobility[2,3]. Our case illustrates the limitations of standard exposure techniques (such as caps or forceps) in mobile or retractable lesions, and the need to resort to advanced traction systems.

The use of the Mantis™ clip as a traction tool is an example of a successful "off-label" application. The traction provided facilitated assessment of the adjacent tissue and allowed for safe and controlled EMR.

Unlike thread-based clips or systems such as the S-O clip (a spring-loaded clip specifically designed for traction)[7], the Mantis™ clip offers a surgical advantage as a "through-the-scope" (TTS) device that enables the "hold-and-drag" technique without the need for external accessories[5,6]. Its TruGrip™ tips and rotational capability facilitate a firm anchor in the adjacent healthy mucosa, allowing for stable displacement and exteriorization of the tissue[5].

While methods such as cap suction may be useful for small areas that are difficult to elevate, they carry an inherent risk of muscle layer injury if not properly controlled[3]. In comparison, the Mantis™ clip allows for more precise and controlled traction, serving as a cost-effective alternative to more complex devices such as the over-the-scope (OTS) clip, which, although excellent for closing large defects, lacks the repositioning versatility offered by the Mantis™ during the lesion exposure phase[8].

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This case demonstrates that devices designed for approximation and closure, thanks to their gripping and control mechanisms, can be effectively repurposed as traction tools, expanding the range of tools available to the endoscopist when faced with complex anatomical barriers. The ability to expose the lesion in a stable and safe manner minimizes the risk of incomplete resection, a crucial factor in preventing recurrences.

Prospective studies are needed to compare the efficacy, safety, and cost-effectiveness of the Mantis™ clip with other traction devices available on the market.

Conclusion

The Mantis™ clip proved to be an effective traction tool for exposing hard-to-reach and highly mobile colorectal lesions, such as those located at the ileocecal valve. Its ability to provide continuous, controlled traction optimizes visualization and facilitates the planning and execution of endoscopic resection.

Access the video

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BILIARY HAMARTOMATOSIS: THE DIAGNOSTIC CHALLENGE BEHIND AN INCIDENTAL FINDING.

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Abstract

Multiple biliary hamartomas, or Von Meyenburg complexes, are uncommon benign malformations of the intrahepatic bile ducts, typically asymptomatic and identified incidentally. Their principal diagnostic challenge is differentiation from small multifocal hepatic metastases.

We report the case of a 62-year-old woman presenting with cholestatic-pattern elevation of liver enzymes, pruritus, and chronic liver disease with significant fibrosis. Cross-sectional imaging demonstrated several subcentimeter hepatic lesions with arterial-phase hyperenhancement, accompanied by persistently elevated CA 19-9 levels. Histological examination of a liver biopsy established the diagnosis of multiple biliary hamartomatosis.

Although CA 19-9 may be chronically elevated in the absence of malignancy, isolated cases of progression to intrahepatic cholangiocarcinoma have been documented in patients with underlying chronic liver disease, thereby supporting individualized surveillance strategies. Overall, biliary hamartomatosis is associated with a favorable clinical course.

Keywords: biliary hamartomas, hepatic metastases, chronic liver disease.

Introduction

Multiple biliary hamartomas, also known as Von Meyenburg complex, are rare benign malformations that originate from the embryonic ductal plate.[1]. They are usually diagnosed incidentally on imaging studies, as most patients remain asymptomatic[2].

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In some cases, they may cause elevated transaminases, pruritus, or be associated with chronic liver disease, and may lead to portal hypertension. Additionally, an association with hepatic and renal polycystic disease has been described[2].

The main differential diagnosis is multiple small liver metastases. The prognosis, however, is usually favorable.[2,3].

Clinical case

A 62-year-old woman with a personal history of hypothyroidism and hypercholesterolemia, occasional alcohol consumption, and under follow-up since 2020 for hypertransaminasemia with a cholestatic profile and pruritus. Chronic liver disease with significant fibrosis was documented (Fibroscan: 18.8 kPa). During the etiological workup, multiple subcentimeter-sized hepatic FLL were identified that were hyper-enhancing in the arterial phase and exhibited nonspecific behavior, with no apparent radiological signs of malignancy; additionally, the CA 19-9 marker level has been around 200 U/mL since the start of the workup. Finally, a liver biopsy was performed, revealing histological findings consistent with multiple biliary hamartomas associated with nodular regenerative liver changes.

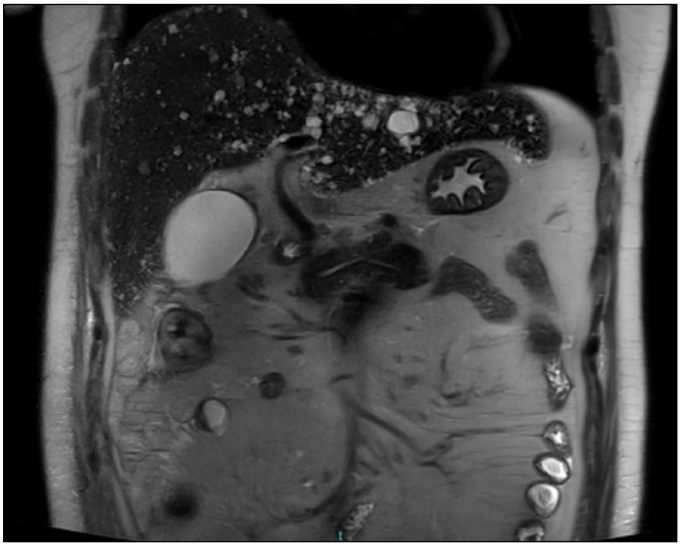

Figure 1. ***Multiple hyperintense lesions in the arterial phase.***

Discussion

Biliary hamartomas can be located in any segment of the liver, although they tend to occur more frequently in the peripheral regions. They are usually small, measuring less than 1.5 cm in most cases[1,2]. In their evaluation, the differential diagnosis must be considered against multiple cystic lesions, small, diffusely distributed metastases, infiltrative-pattern hepatocellular carcinoma, disseminated microabscesses,

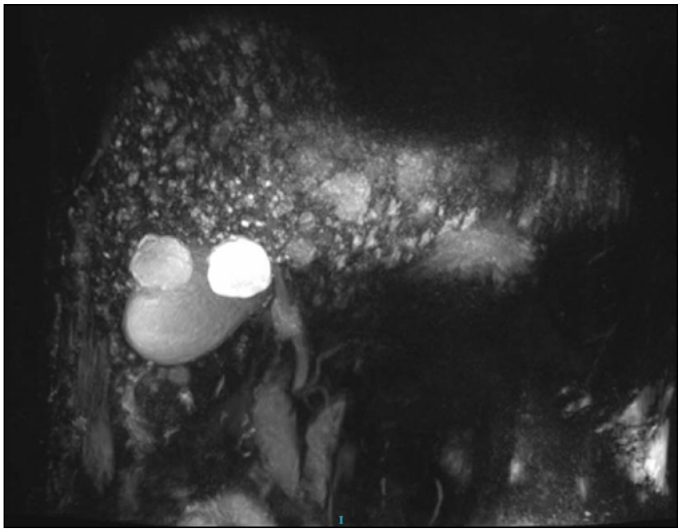

Figure 2. ***MR Cholangiography.***

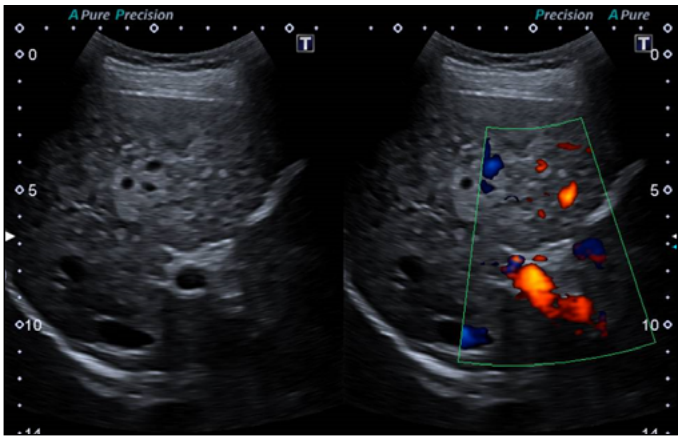

Figure 3. ***Space-occupying lesions on the liver with irregular morphology.***

and multiple nodular steatosis.[2,3]. On computed tomography, they appear as hypodense areas. On gadolinium-enhanced magnetic resonance imaging, they are characterized by T1-hypointense and T2-hyperintense signals.[1,2].

The CA 19-9 tumor marker is nonspecific and may remain persistently elevated in patients with hamartomatosis without indicating malignancy. However, exceptional cases of transformation into intrahepatic cholangiocarcinoma have been described in the literature, particularly in patients with underlying chronic liver disease[3], which warrants individualized clinical follow-up in certain patients.

In general, biliary hamartomatosis does not require specific treatment, except in symptomatic patients (e.g., right upper quadrant pain or pruritus) or in those in whom a complication is suspected. The prognosis is usually favorable, although it is prudent to maintain clinical surveillance in patients with associated advanced liver disease[3].

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