Article:
Mariette, C, Carneiro, F, Grabsch, HI et al. (3 more authors) (2019) Consensus on the pathological definition and classification of poorly cohesive gastric carcinoma. Gastric Cancer, 22 (1). pp. 1-9. ISSN 1436-3291

https://doi.org/10.1007/s10120-018-0868-0

Gastric Cancer

CONSENSUS ON THE PATHOLOGICAL DEFINITION AND CLASSIFICATION OF POORLY COHESIVE GASTRIC CARCINOMA

--Manuscript Draft--

Manuscript Number:	GCAN-D-18-00158R2
Full Title:	CONSENSUS ON THE PATHOLOGICAL DEFINITION AND CLASSIFICATION OF POORLY COHESIVE GASTRIC CARCINOMA
Article Type:	Others
Manuscript Classifications:	1.008: Classifications; 4.001: Morphologic; 4.003: Immunohistochemistry
Keywords:	gastric cancer; poorly cohesive sub-type; signet ring cell histology
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Funding Information:	
Abstract:	Background and aims: Clinicopathological characteristics of gastric cancer (GC) are changing, especially in the West with a decreasing incidence of distal, intestinal type tumours and a corresponding increasing proportion of tumours with Laurén diffuse or WHO Poorly Cohesive (PC) including Signet Ring Cell (SRC) histology. In order to assess the behavior and the prognosis of these GC subtypes, the standardization of pathological definitions is needed. Methods: An expert team belonging to the European Chapter of International Gastric Cancer Association identified 11 debated topics on pathological classifications used for PC and SRC GC. The topics were discussed during a dedicated Workshop held in Verona in March 2017. Then, through a Delphi method, Consensus statements for each topic were elaborated. Results: A Consensus was reached on the need to classify gastric carcinoma according to the most recent edition of the WHO classification that is currently WHO 2010. Moreover, in order to standardize the definition of SRC carcinomas, the proposal that only WHO PC carcinomas with more than 90% poorly cohesive cells having signet ring cell morphology have to be classified as SRC carcinomas was made. All other PC non-SRC types have to be further subdivided into PC carcinomas with SRC component (<90% but >10% Signet Ring Cells) and PC carcinomas Not Otherwise Specified (<10% Signet Ring Cells). Conclusion: The reported Consensus statements clarify some debated topics on pathological classifications used for PC and SRC GC. It would help the generation of strong evidences on biological and prognostic differences of these GC subtypes.

Additional Information:	
Question	**Response**
Is the work reported on in your paper a clinical study?	No
Is the work reported on in your paper a prospective study?	No
Have you already obtained approval for your work from the IRB (Institutional Review Board)?	No
Do you agree to submit the original protocol upon request from the editorial committee?	Yes

We thank the Editors and the Reviewers for the time and efforts made to revise our manuscript. As suggested, we looked at the figures by the Reviewer #2. You can find below our response to the specific Reviewer's requests.

Reviewer #2: General comments . The authors revised their manuscript according to the reviewers' comments as much as possible. However, there is a minor concern regarding the definition. Is poorly cohesive carcinoma with intracytoplasmic lumen which mimics to true "signet ring" (Figure A, arrows) signet-ring cell carcinoma? In addition, can carcinoma cells consisting of a ubiquitous oval nuclei and relatively abundant mucus (Figure B, arrows) be called as signet-ring cell carcinoma?

We deeply thank the Reviewer for this important comment. Indeed, the reason to make some consensus on morphology of SRC is to make better categories to study follow-up/ therapies etc. As for the definition of what we call a signet ring cell on an individual cell level, it would be very difficult to say until we have more detailled molecular data. Also, we think that one cannot decide on the % of SRCs of a tumour *using high power figures. However, to make an attempt to answer to the Reviewer's* specific requests:

1) In figure A you can see these cells that have a big vacuole in the cytoplasm surrounded by a mor bubbly cytplasm and the nucleus on one side although not really squeezed to a signet ring shape. They are for sure not classical signet ring cells, as such this tumour (A) would fall in the category of PC <10% SRC.
2) In figure B, at the right bottom you can just see what we would call a classical signet ring cell, while the neighbouring cells are likely signet ring cells in development. Indeed, we think that it takes some time to accumulate the mucin in the cytoplasm to squeeze the nucleus to the edge. This tumour (B) would fall in the category of poorly cohesive carcinoma with features of 10-90% signet ring cells.

August, 7th 2018

Dear Editor,

We appreciate your Journal's interest in our manuscript. We are aware that there are some differences in the interpretation of gastric cancer morphology between the Eastern and Western pathologist. Indeed, one of the main reasons to make some consensus on morphology of SRC is to make better categories to study follow-up and therapies of these tumours also across world regions. I hope this further revision would satisfy the Editors and Reviewers requests.

Please, find enclosed our response to the reviewers' comments and the revised manuscript. Again, we appreciate your thoughtful consideration of our paper and we look forward to future correspondence.

Best regards,

Prof. Giovanni de Manzoni

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CONSENSUS ON THE PATHOLOGICAL DEFINITION AND CLASSIFICATION OF POORLY COHESIVE GASTRIC CARCINOMA

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RUNNING TITLE: Standardization of definitions and classification used for poorly cohesive and signet ring cell gastric carcinoma

KEY WORDS: gastric cancer ; Poorly Cohesive sub-type; Signet Ring Cell histology;

WORD COUNT: 2601

TOTAL NUMBER OF TABLES: 2

TOTAL NUMBER OF FIGURES: 3

FINANCIAL SUPPORT: None

CONFLICT OF INTEREST: None

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ABSTRACT

Background and aims: Clinicopathological characteristics of gastric cancer (GC) are changing, especially in the West with a decreasing incidence of distal, intestinal type tumours and a corresponding increasing proportion of tumours with Laurén diffuse or WHO poorly cohesive (PC) including signet ring cell (SRC) histology. In order to accurately assess the behavior and the prognosis of these GC subtypes, the standardization of pathological definitions is needed.

Methods: A multidisciplinary expert team belonging to the European Chapter of International Gastric Cancer Association (IGCA) identified 11 topics on pathological classifications used for PC and SRC GC. The topics were debated during a dedicated Workshop held in Verona in March 2017. Then, through a Delphi method, consensus statements for each topic were elaborated.

Results: A consensus was reached on the need to classify gastric carcinoma according to the most recent edition of the WHO classification which is currently WHO 2010. Moreover, in order to standardize the definition of SRC carcinomas, the proposal that only WHO PC carcinomas with more than 90% poorly cohesive cells having signet ring cell morphology have to be classified as SRC carcinomas was made. All other PC non-SRC types have to be further subdivided into PC carcinomas with SRC component (<90% but >10% SRCs) and PC carcinomas not otherwise specified (<10% SRCs).

Conclusion: The reported statements clarify some debated topics on pathological classifications used for PC and SRC GC. As such, this consensus classification would allow the generation of evidence on biological and prognostic differences between these GC subtypes.

INTRODUCTION

Despite a declining incidence, Gastric Cancer (GC) is still one of the major causes of cancer death worldwide [1]. Evidence has accumulated over the last decades that clinicopathological characteristics of GC are changing, especially in the West [2-4] with a decreasing incidence of distal, intestinal type tumours and a corresponding increasing proportion of tumours with Laurén diffuse [5] or WHO [6] poorly cohesive (PC) including signet ring cell (SRC) histology [2-4].

Conflicting data exist about the prognostic relevance of SRC histology [7-8]. While some authors report a relationship between SRC histology and poor prognosis [7], other studies have not confirmed this finding [8]. More recently, some comparative studies from Western and Asian authors [9, 10] suggested that the prognostic impact of SRC histology depends on the stage of the disease, being favourable in early stages but adverse in advanced tumour stages. One of the main reasons for these inconsistent findings over the relationship between SRC and prognosis appears to be a lack of standardization of GC histological subtype definitions. The 2010 WHO classification [6] defines PC tumours as GC composed of isolated or small groups of tumour cells. If neoplastic cells with SRC morphology predominate in the tumour, the tumour is defined as SRC carcinoma. In reality, the terms Laurén "diffuse type", "poorly cohesive" and "signet ring cell" GC are often used indiscriminately. As a consequence, tumours having major and minor SRC components may have been inappropriately considered together in comparative studies [11].

Standardization of terminology and classifications is a crucial step in order to accurately assess epidemiological trends and to allow prediction of prognosis and/or response to chemotherapy of GC patients with SRC as well as PC non-SRC tumours compared to other GC subtypes and to design tailored treatment strategies. In order to reach a consensus on the pathological classification of PC and SRC GC, a multidisciplinary expert team belonging to the European Chapter of International Gastric Cancer Association (IGCA) attended a dedicated Workshop in Verona in March 2017.

METHODS

The methodology of this project was similar to that of other multicentric consensus reports [12,13]. After establishing the purpose of the project, a restricted working group (RWG) of the European Chapter of IGCA identified areas of uncertainty about the histopathological definitions and classifications of PC and SRC gastric cancers in order to define the topics for debate.

Next, an expanded working group (EWG) of European experts (**Table 1**), was invited to take part in a dedicated workshop held in Verona, Italy, on the 17th of March, 2017. During the Workshop, the previoulsy identified topics were discussed and a draft statement in response to each topic was recorded.

Each expert was asked to comment and suggest modifications to the draft statements through a Delphi method implementation. These suggestions were made available to the other experts in a series of web-based discussion rounds for further discussion and definitive approval. The grade of expert agreement to each statement is reported.

RESULTS

Consensus statements are reported as follows. There was unanimous agreement to each statement, except for the statement 5 where one of the experts disagreed.

TOPIC 1

What is the unequivocal definition of a signet ring cell (SRC)?

STATEMENT 1

The definition of a signet ring cell is that of a cell with ample cytoplasmic mucin which appears optically clear on Haematoxylin Eosin (HE) staining and an eccentrically placed nucleus [6]. All other poorly cohesive cancer cells that do not display this specific morphology should be classified as poorly cohesive cells (PC) not otherwise specified (NOS).

TOPIC 2

Is a cell with signet ring morphology always a malignant cell? What are the main differential diagnoses of cells with poorly cohesive/signet ring cell morphology?

STATEMENT 2

No, a cell with signet ring morphology is not always malignant. There are benign lookalikes that can mimic signet ring cell carcinoma which are illustrated in **Panel Figure 1 and Figure 2** [14]. Furthermore, dystrophic goblet cells, non-neoplastic epithelial cells associated with ulceration and ischaemia, macrophages or mesothelial cells in cytology preparations can look like signet ring cells.

Apart from benign signet ring cell change, lymphoma, poorly differentiated intestinal gastric adenocarcinoma, neuroendocrine tumours, metastatic lobular breast cancer, ovarian cancer and melanoma should be considered in the differential diagnosis of signet ring cell carcinoma.

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TOPIC 3

Can SRC carcinoma be identified by other means than HE morphology? Are there routinely used immunohistochemical (IHC) marker and if so, what are they?

STATEMENT 3

Currently there are no specific IHC markers used routinely. E-cadherin or cytokeratin subtyping do not aid in the identification of signet ring cells. However, histochemical staining for mucin (AB-PAS) can be used to confirm the presence of mucin in signet ring cells.

TOPIC 4

Currently, the terms "diffuse type" cancers according to Laurén classification, "poorly cohesive carcinomas" according to the WHO classification 2010, "signet ring cell"

carcinomas, and *"linitis plastica"* are used indiscriminately. How can terminology used to describe the histology of these tumours be standardized?

STATEMENT 4

In the pathology report, gastric adenocarcinoma should be classified according to the most recent edition of the WHO classification which is currently the 4th ed published in 2010 [6]. The Laurén *"diffuse"* type [5] corresponds to the WHO category of *"*poorly c*ohesive"* carcinomas.

The WHO 2010 category of PC carcinoma includes SRC which is defined as PC carcinoma that contains predominantly or exclusively signet ring cells (See Statement 5).

The term *"linitis plastica"* should only be used for the description of the macroscopic characteristics of the tumour.

TOPIC 5

A SRC carcinoma is defined according to the WHO as PC carcinoma containing predominantly or exclusively signet ring cells. Should an internationally standardized method be used, to define the proportion of signet ring cells required to subclassify tumours with signet ring cells?

STATEMENT 5

In order to standardize the definition of SRC cancers, we propose that only WHO PC carcinomas with more than 90% poorly cohesive cells having classical signet ring cell morphology should be classified as SRC carcinomas.

We propose to use the following subclassification of PC and SRC carcinomas:

- Signet ring cell (SRC) type (>90% of signet ring cells)
- Combined poorly cohesive NOS and SRC Carcinoma (PC-NOS/SRC; <90% but >10% of signet ring cells)
- Poorly cohesive NOS (PC-NOS; <10% of signet ring cells)

We believe that by using the above categories of poorly cohesive carcinomas, and comparing tumours with almost exclusive (>90%) signet ring cells to those with lower (<90% but >10% and <10%) proportion of signet ring cells in retrospective and prospective studies, the prognostic differences of PC tumours with different proportion of cells with signet ring morphology can be accurately investigated.

It is important that these categories/subclassification are only used for PC and SRC carcinomas. Mucinous cancers are characterized by the presence of extracellular mucin in more than 50% of the tumour area. Even if mucinous cancers contain signet ring cells, they should not be classified as poorly cohesive/signet ring cell carcinomas as mucinous cancers have different biology and prognosis.

TOPIC 6

How big is the discrepancy between histological tumour type in endoscopic biopsies and resected specimen in gastric cancer using the current WHO classification? Do you believe that this discrepancy is larger for PC / SRC carcinomas?

STATEMENT 6

Due to the uncertainty about the definition used when reporting results, it is currently unclear whether there is a discrepancy between biopsy classification and resection specimen classification. We therefore believe that it is necessary to report in PC carcinoma whether signet ring cells are present in specimens or not. The concordance between preoperative biopsies and resected specimens according to the proposed definitions (statement 5) should be assessed.

TOPIC 7

Is the determination of the pathological depth of invasion (pT category) in PC/SRC

carcinomas, in particular regarding the involvement of the serosa, more difficult than in other histological types of gastric cancer?

STATEMENT 7

There are more difficulties in determining the pathological T category in PC and SRC carcinomas. Immunohistochemical staining for cytokeratin does not help as the mesothelial cells of the serosa also express cytokeratins. Elastica stains may be helpful to identify the location of the serosa.

TOPIC 8

Is the type of stroma reaction the same in all SRC cancers? If not, do you think this could have a prognostic impact?

STATEMENT 8

The stroma reaction is not the same in all PC and SRC carcinomas. The stroma reaction may change depending on depth of tumour invasion. It is likely that the type of stroma reaction has a prognostic impact, but available data are limited [15].

TOPIC 9

Does neoadjuvant treatment modify gastric cancer histopathological phenotype? Can a histopathological response to neoadjuvant chemotherapy (tumour regression grade) be established in SRC carcinomas in the same way as in non-SRC carcinomas? Are there specific pathological criteria to assess the response to neo-adjuvant treatments in SRC ~~cancers~~ carcinoma?

STATEMENT 9

Apart from seeing regressive features like fibrosis and necrosis, there is no definitive evidence that the histological phenotype of cancer cells change after neoadjuvant chemotherapy.

In GC patients who received neoadjuvant therapy, we only have the pretreatment diagnostic biopsy to determine the tumour phenotype. There is no evidence yet that the tumour phenotype changes after chemo(radio)therapy. By reviewing slides of resected specimens from clinical trials comparing surgery alone to neoadjuvant therapy followed by surgery, we could evaluate the impact of neoadjuvant therapy on the histological tumour phenotype in gastric adenocarcinoma including in tumours with PC/SRC histology classified on the pretreatment diagnostic biopsies.

At the moment, there are no specific pathologic criteria to assess the response to neoadjuvant treatment in poorly cohesive and signet ring cell types.

Tumour regression grade according to Becker [16] or Mandard [17] is currently reported in pathological reports in most Western countries. It is noteworthy that pathologists have difficulties in particular in PC GC in differentiating treatment naïve desmoplastic stroma from treatment induced fibrosis. It therefore appears necessary to develop specific pathologic regression systems for PC and SRC tumours.

Of note, these pathologic regression systems should include not only regression grading for the primary tumour but also for the lymph nodes. Indeed, for oesophageal and cardia cancer [18-24] the prognostic relevance of nodal response to preoperative treatments has already been demonstrated, and this is likely to be significant in gastric cancer, too.

It would be very interesting to evaluate the rates of pathologic tumour and nodal response to preoperative treatment according to the proportion of signet ring cells, i.e. based on the classification proposed in Statement 5.

TOPIC 10

Is it possible to find signet ring cells also in the context of tubular or papillary gastric adenocarcinoma? If yes, how do you classify this tumour?

STATEMENT 10

The WHO classification 4th ed. [6] defines *'*mixed adenocarcinoma*' as* a tumor with a

discrete component of tubulo-papillar and a poorly cohesive-SRC component. It means that each component should be clearly separate. There is currently no cut-off defined with respect to percentage of each component for a tumour to be classified as mixed adenocarcinoma. However, if only rare signet ring cells/rare poorly cohesive cells are present, for example at the invasive edge, the tumour should still be classified as tubular or papillary tumour.

TOPIC 11

In case of WHO mixed type gastric cancers, is there pathological evidence that the PC/SRC component is more 'aggressive' showing a higher frequency of lymph node metastases?

STATEMENT 11

Both, the tubulo-papillary and PC-SRC components may be aggressive.

The two components have different pathways of tumour dissemination with the tubulo-papillary (Laurén: intestinal type) component spreading more frequently by angioinvasion, while the PC-SRC (Laurén: diffuse type) component tend to metastasise to the peritoneum [25].

Currently, one can only speculate that the cumulative effect of the adverse behaviours of intestinal and diffuse type gastric carcinoma is responsible for the greater biological aggressiveness of mixed type gastric carcinoma compared to *"pure"* intestinal and diffuse gastric carcinoma [26-33]. The level of existing evidence is too low for a definitive conclusion.

DISCUSSION

The proportion of Laurén diffuse and WHO PC and SRC gastric cancer subtypes have increased in recent years, especially in the West [2-4]. Some studies reported an independent unfavourable prognostic impact of SRC histology compared to other histotypes [7], while others could not confirm this [8]. More recently a stage-dependent prognostic role of SRC has been suggested by Western and Eastern authors [9,10]. Different proportions of early and advanced SRC tumours in the published series may have caused the inconsistency of data reported so far.

Most importantly, there is no standardization in the terminology used to define tumours with signet ring cells and very often the definitions of "diffuse type" cancers according to Laurén classification, "poorly cohesive " and "signet ring cell" gastric carcinomas according to the 2010 WHO classification, or "linitis plastica" are used indiscriminately. Findings reported in comparative studies [7-10] could have been affected by the heterogeneity of SRC and non-SRC cancers. To establish reproducible definitions towards standardised classification of gastric cancer, a European consensus group has produced the definitions described in this paper.

The two key issues for pathologists are firstly, that gastric carcinoma should be classified according to the most recent edition of the WHO classification which is currently WHO 2010 [6]. The Laurén "diffuse" type corresponds to the WHO category of "poorly cohesive" carcinomas.

Secondly, in order to standardize the definition of SRC carcinomas, we propose that only WHO PC carcinomas with more than 90% poorly cohesive cells having signet ring cell morphology should be classified as SRC carcinomas. All other PC non-SRC types should be further subdivided into PC carcinomas with SRC component (<90% but >10% signet ring cells) and PC carcinomas NOS (<10% signet ring cells). This classification reflects the hypothesis that the extent of SRCs may represent a differentiation grade in PC and SRC carcinomas. Studies in Hereditary Diffuse Gastric Cancer (HDGC) suggest that intramucosal lesions morphologically characterized by typical signet ring cells without expression of Ki67 and p53 represent an "indolent" phenotype. By contrast

advanced carcinomas that display an “aggressive” phenotype with positive immunoreaction for Ki67 and p53, are composed of poorly cohesive pleomorphic cells without SRC morphology [34]. A recent study in Korean patients with gastric PC carcinoma subclassified each tumour on the basis of the prevalent histopathological component into “pure” SRC type (signet ring cells > 95%), “pure” PC not otherwise specified (PCC-NOS) type (i.e. no SRC), mixed SRC-predominant type (SRC > PCC-NOS, SRC >50%) or mixed PCC-NOS-predominant type (PCC-NOS >SRC) [35]. A distinct mutation pattern and significant differences in overall survival were reported for “pure” SRC type and “pure” PC not otherwise specified type, with better outcome for the former category. These findings support our proposal to distinguish different subcategories of PC gastric carcinoma. Such classification would allow the generation of evidence on biological and prognostic differences of these tumours according to the proportion of signet ring cells.

In the Japanese pathological classification [36], the poorly differentiated non-solid type (por2) category that substantially corresponds to the WHO category of PC non-SRC type, is considered separately from the SRC type (**Table 2)**. Also, in recent papers, Japanese authors [37] confirm that histopathological features of signet ring cell types differ from those of poorly differentiated (por2) tumours and highlight the need to differentiate them in clinical studies.

It is important that pathologists attempt to subclassify gastric cancer on biopsies (when adequate biopsies are available) and not use the term ‘adenocarcinoma NOS’, since most patients will receive preoperative treatment which may change tumour morphology. Future clinical and translational research should include the creation of specific pathologic regression systems for tumours with PC/SRC, but also a more in-depth analysis of role of stroma reaction and genomic characteristics of these subtypes of gastric cancer.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest

ETHICAL STANDARDS

This article does not contain any studies with human or animal subjects performed by any of the authors. There was no need to get informed consent.

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Acknowledgments

Baiocchi Gian Luca (University of Brescia, Brescia, Italy); Bencivenga Maria (University of Verona, Verona, Italy), Flejou Jean-Francois (Hôpitaux Universitaires Est Parisien, Hôpital Saint-Antoine, Paris, France); Fumaglli Uberto (Spedali Civili, Brescia, Italy); Hoelscher Arnulf (Agaplesion Markus Krankenhaus, Frankfurt, Germany); Iglesias Mar (Hospital Universitario del Mar, Barcelona, Spain); Marrelli Daniele (University of Siena, Siena, Italy); Moenig Stephan (Hôpitaux Universitaires de Genève, Genève, Switzerland); Morgagni Paolo (G.B. Morgagni-L Pierantoni Hospital, Forlì, Italy); Pera Manuel (Hospital Universitario del Mar, Barcelona, Spain);

Piessen Giullaume (University Hospital of Lille, Lille, France); Reim Daniel (Klinikum Rechts der Isar der Technischen Universität München, Munich, Germany); Renaud Florence (University Hospital of Lille, Lille, France); Roviello Franco (University of Siena, Siena, Italy); Saragoni Luca (G.B. Morgagni-L. Pierantoni Hospital, Forlì, Italy); Scarpa Aldo (University of Verona, Verona, Italy); Schneider Paul (Hirslanden Hospital Zurich, Switzerland); Tomezzoli Anna (Verona University Hospital, Verona, Italy); Vieth Michael (Klinikum Bayreuth, Bayreuth, Germany); Wotherspoon Andrew (The Royal Marsden NHS Foundation Trust, London and Surrey, United Kingdom); Zamboni Giuseppe (Sacro Cuore-Don Calabria Hospital, Negrar, Italy).

Figures Legend

Panel Figure 1: Mimickers of signet ring cell carcinoma in gastric mucosa

A – Vacuolization of the foveolar epithelium; B – Hyperplastic polyp with globoid change; C – Glassy cell change; D – prominent mucous neck cells; E – Ischemic/ autolytic change with loss of epithelial cells and signet cell change in a hyperplastic polyp; F – Neuroendocrine tumor; G – Low grade dysplasia and dystrophic intestinal metaplasia; H – Xanthoma (H&E, original magnifications 200-400x).

Figure 2 Carcinoma-like signet ring cells in MALT lymphoma: multiple single and clusters of SRCs characterized by abundant pale cytoplasm and a small peripheral nucleus, intermingled with diffuse infiltrate of marginal-zone B cells.

Panel Figure 2: Poorly cohoesive gastric carcinoma, examples of morphology

A – Signet ring cell carcinoma (SRCC) (>90% of signet ring cells): classical signet ring cells are seen at the superficial layer of gastric mucosa ; B – Combined PCC-NOS and SRCC (PCC-NOS/ SRC) (<90% but >10% of signet ring cells): this case has two components, the superficial part is composed of classical signet ring cells and the deeper part is composed by poorly cohesive, non-signet ring cells; C – Combined PCC-NOS and SRCC (PCC-NOS/ SRC) (<90% but >10% of Signet Ring cells): in this case, the two cell types (signet ring and poorly cohesive cells) are intermingled; D – Poorly cohesive carcinoma NOS (PCC-NOS) (<10% of signet ring cells): the poorly cohesive, non-signet ring cells, are invading the muscle layer (H&E, original magnifications 200-400x).

Table 1: List of participants at the Verona Workshop on Poorly Cohesive and Signet Ring Cell Gastric Cancer.

NAME		COUNTRY	SPECIALITY
Allum	William	United Kingdom	Surgeon
Baiocchi	Gian Luca	Italy	Surgeon
Carneiro	Fatima	Portugal	Pathologist
De Manzoni	Giovanni	Italy	Surgeon
Flejou	Jean-Francois	France	Pathologist
Fumagalli	Uberto	Italy	Surgeon
Grabsch	Heike	Netherlands	Pathologist
Hoelscher	Arnulf	Germany	Surgeon
Iglesias	Mar	Spain	Pathologist
Mariette	Christophe	France	Surgeon
Marrelli	Daniele	Italy	Surgeon
Moenig	Stefan	Switzerland	Surgeon
Morgagni	Paolo	Italy	Surgeon
Pera	Manuel	Spain	Surgeon
Piessen	Guillaume	France	Surgeon
Reim	Daniel	Germany	Surgeon
Renaud	Florence	France	Pathologist
Roviello	Franco	Italy	Surgeon

Saragoni	Luca	Italy	Pathologist
Scarpa	Aldo	Italy	Pathologist
Schneider	Paul	Switzerland	Surgeon
Tomezzoli	Anna	Italy	Pathologist
Vanderpost	Chella	Netherlands	Pathologist
Vieth	Michael	Germany	Pathologist
Wotherspoon	Andrew	United Kingdom	Pathologist
Zamboni	Giuseppe	Italy	Pathologist

Table 2 – Comparison of different classifications of gastric cancer (Laurén, Nakamura, WHO and Japanese classifications)

Laurén (1965)	**Nakamura** (1968)	**WHO** (2010)	**Japanese classification** (2017)
Intestinal	Differentiated	Common type: Papillary Tubular	Common type: Papillary: pap Tubular 1 (well-differentiated): tub1 Tubular 2 (moderately-differentiated): tub2
Intestinal/diffuse	Differentiated/ Undifferentiated	Common type: Mucinous	Common type: Mucinous
Diffuse	Undifferentiated	Common type: Poorly cohesive, SRC phenotype Poorly cohesive, other cell types	Common type: SRC carcinoma: sig Poorly 2 (non-solid type): por2
Mixed	Undifferentiated	Common type: Mixed	Description according to the proportion (*e.g.* por2>sig>tub2)
Indeterminate	Undifferentiated	Common type: Poorly differentiated tubular (solid) carcinoma Special type: Undifferentiated carcinoma	Common type: Poorly 1 (solid type): por1 Special type: Undifferentiated carcinoma

Figure

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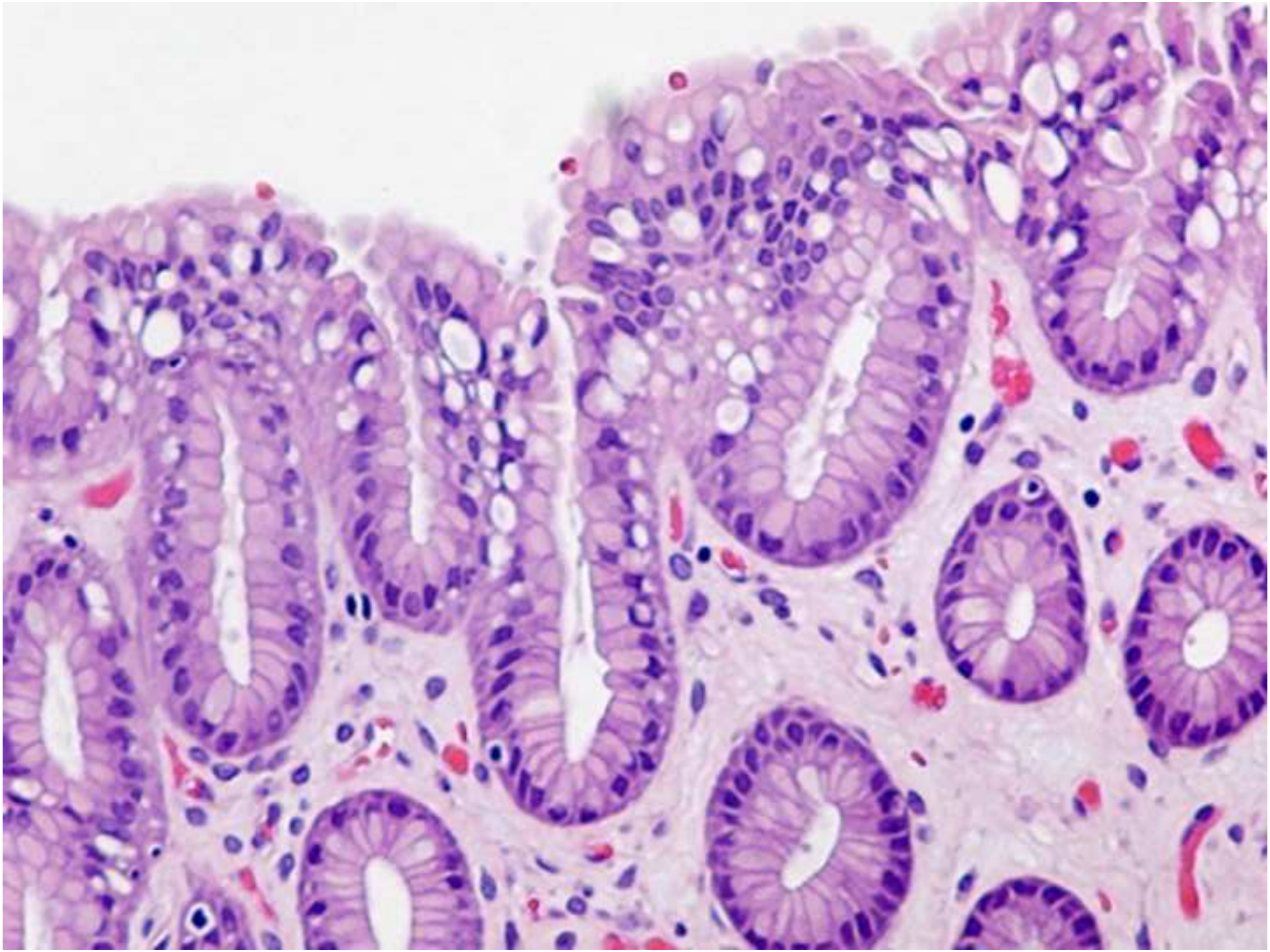

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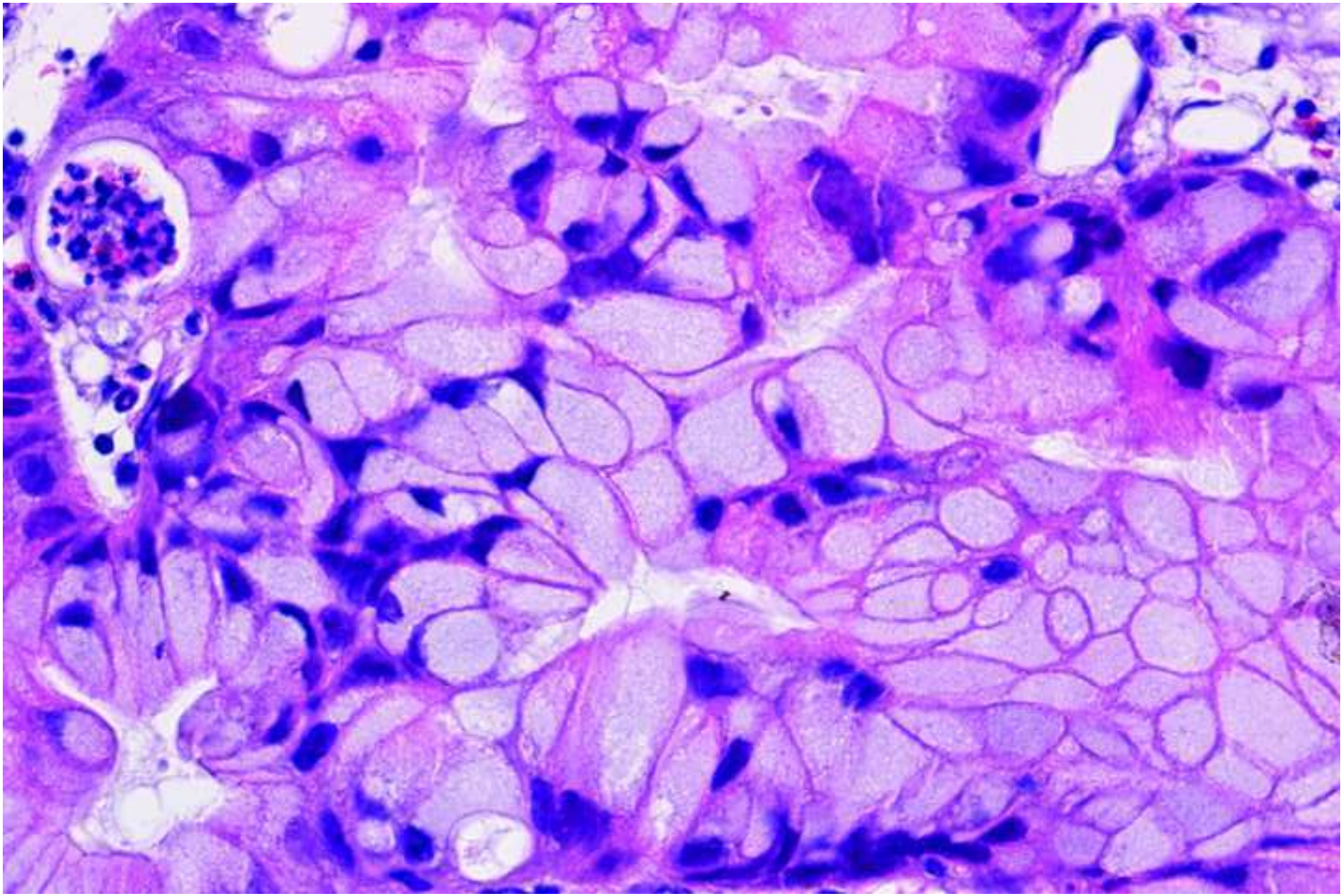

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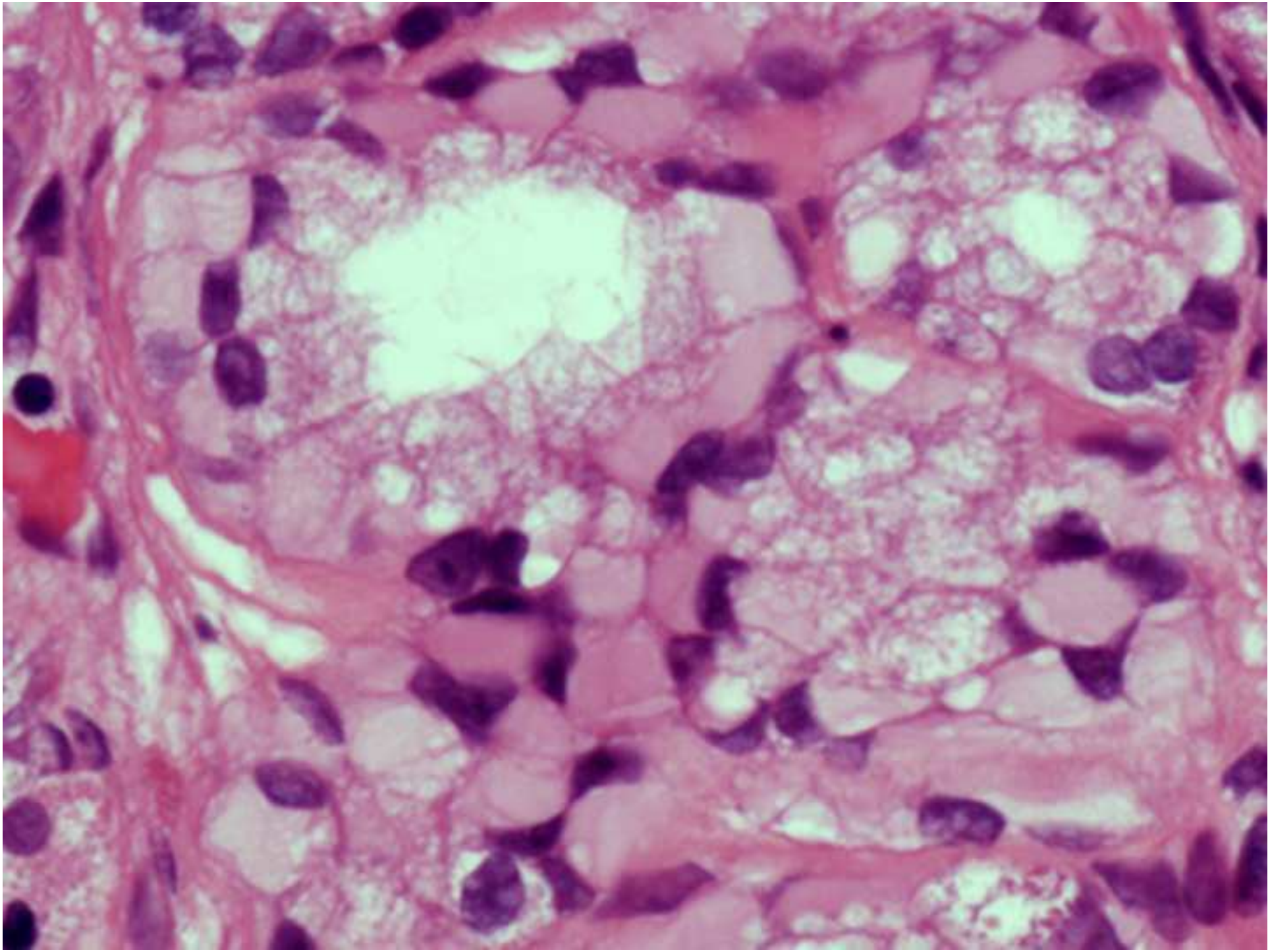

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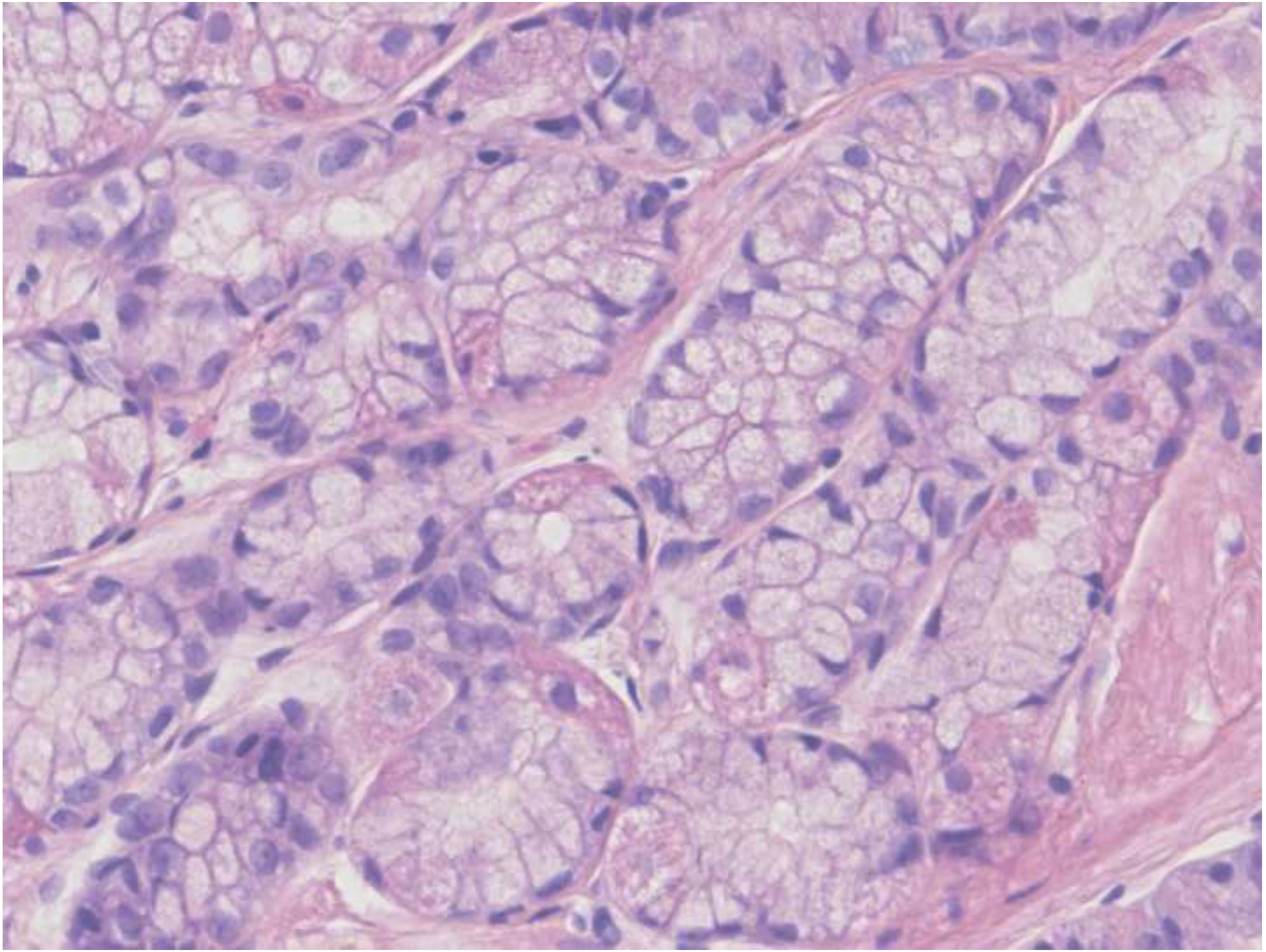

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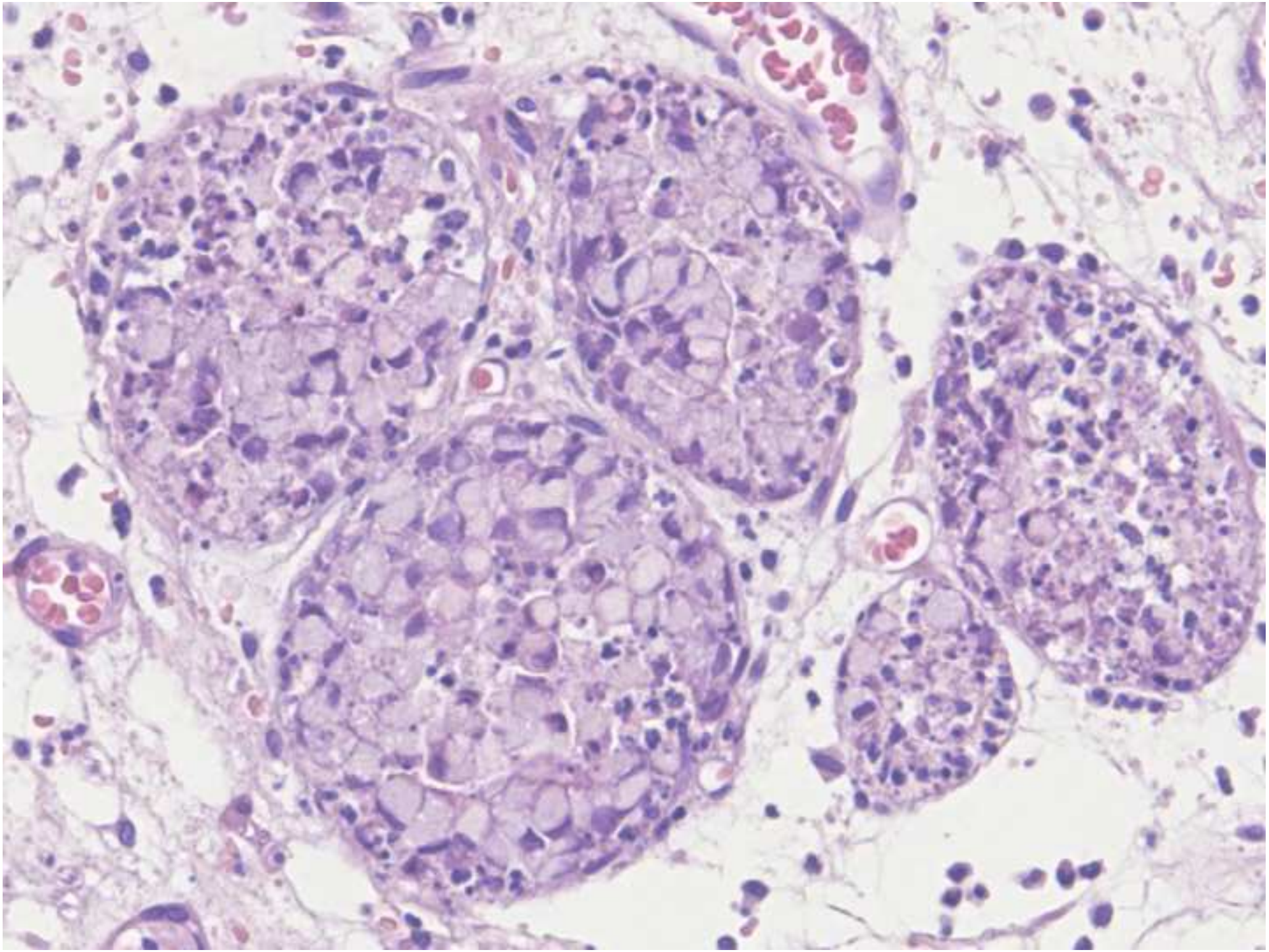

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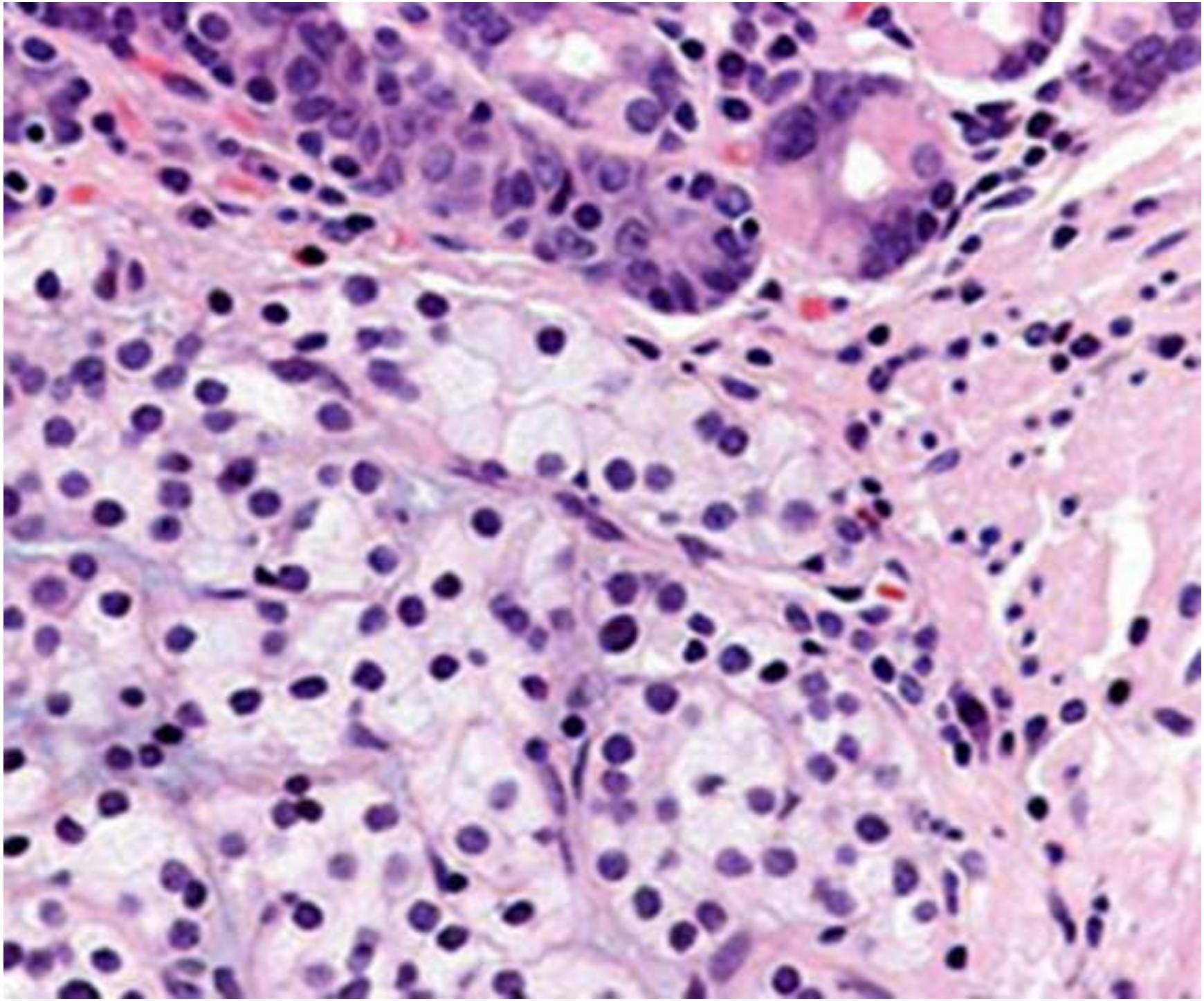

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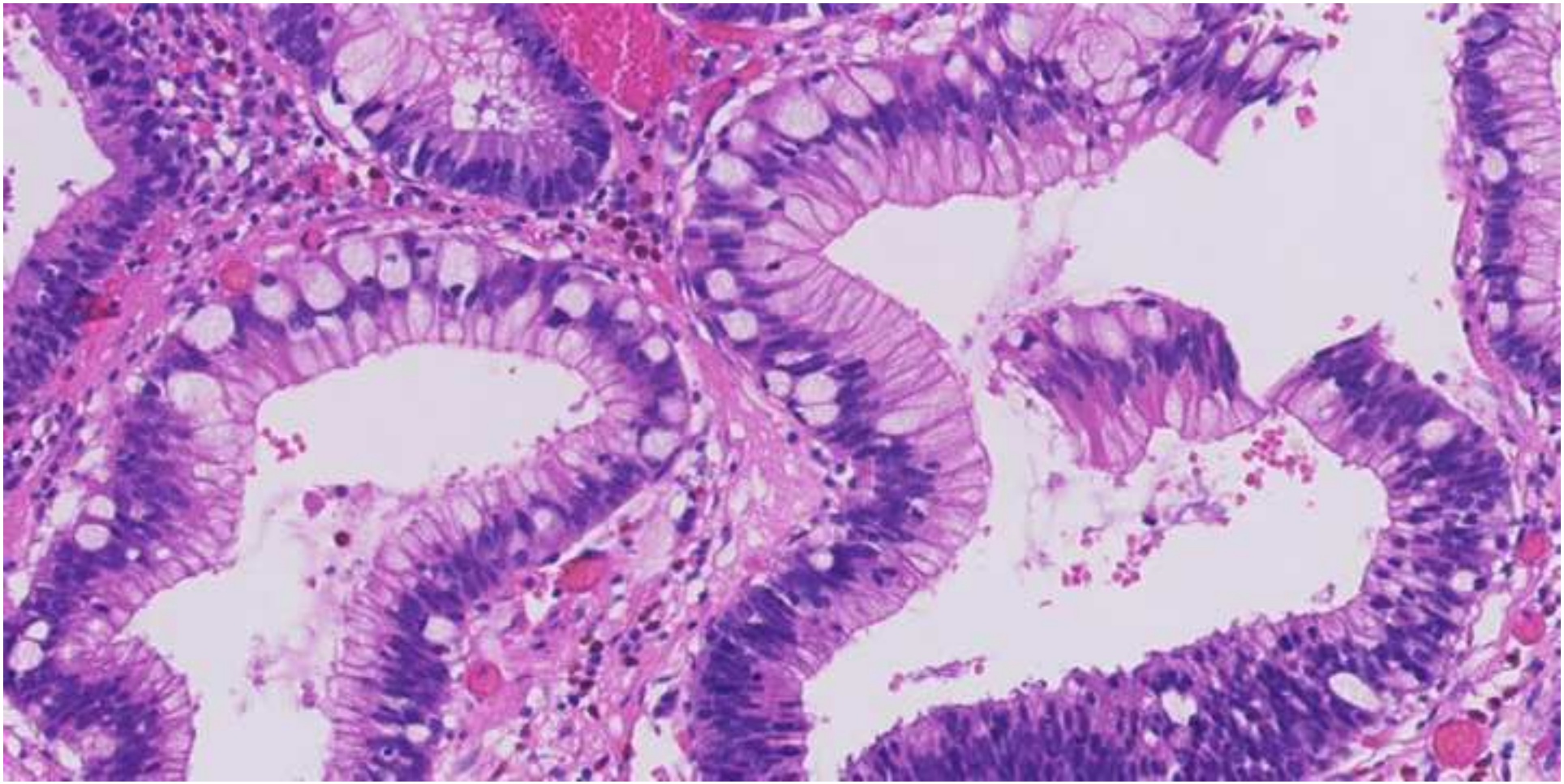

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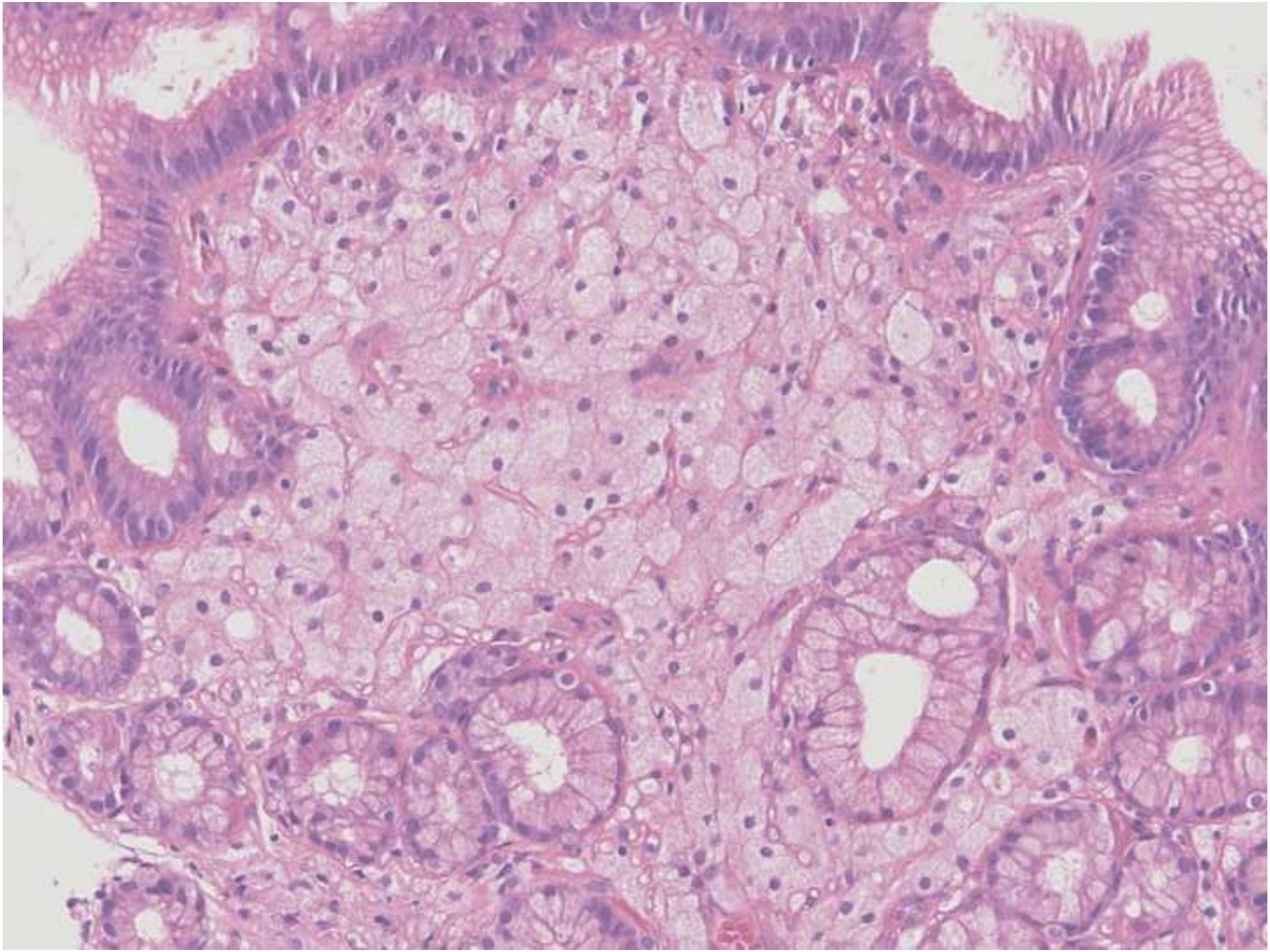

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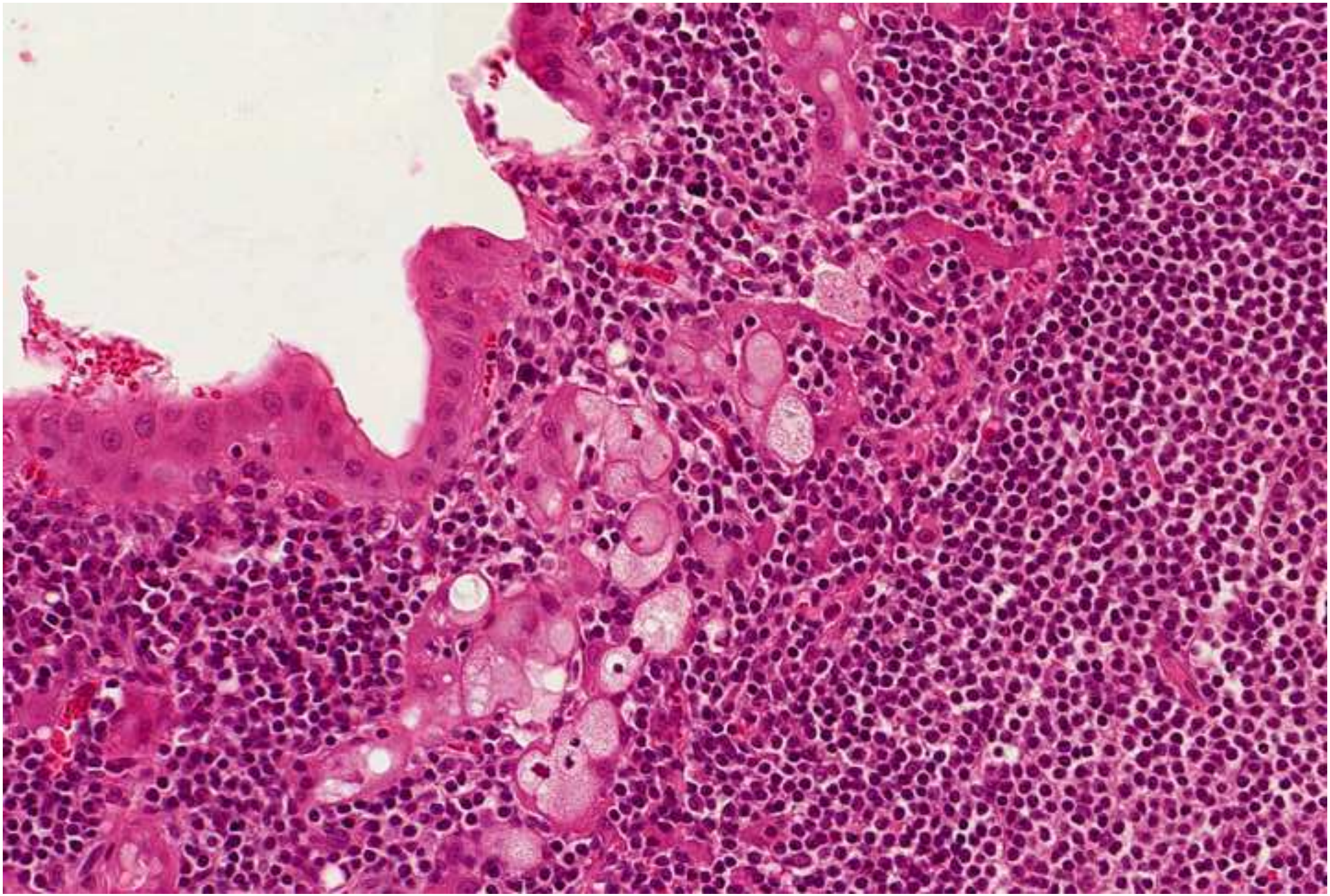

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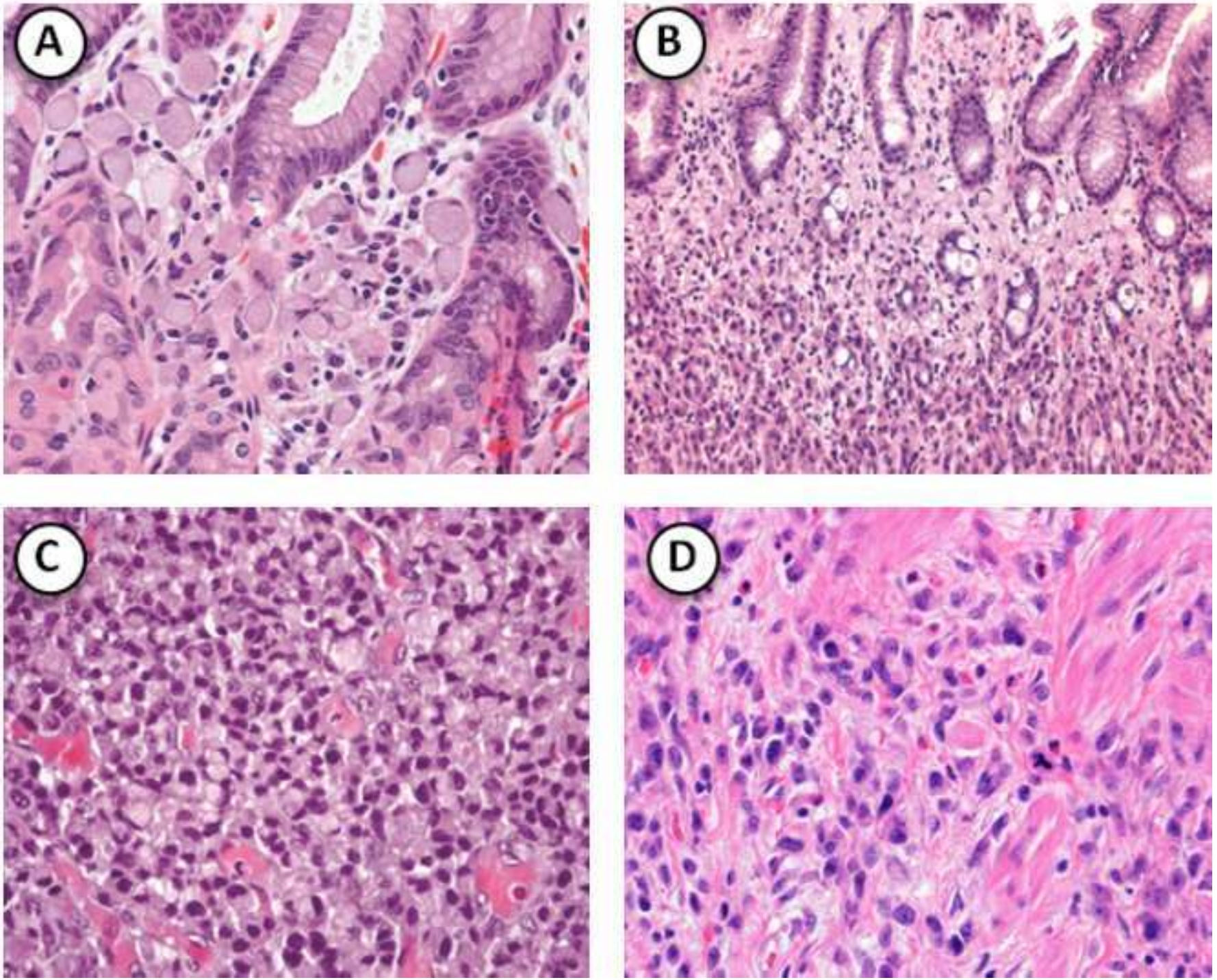

MINIABSTRACT

This Consensus clarifies some debated topics on pathological classifications used for Poorly Cohesive and Signet Ring Cell Gastric Cancer. As such, it would allow the generation of strong evidences on biological and prognostic differences of these GC subtypes.

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