Thymoma-associated multiorgan autoimmunity with exclusive gastrointestinal tract involvement: case report and review of the literature.

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ABSTRACT

Thymoma-associated multiorgan autoimmunity (TAMA) is a recently delineated and rare paraneoplastic syndrome documented in patients with thymoma. The disorder is characterized by graft-versus-host disease (GvHD)-like pathology affecting the skin, gastrointestinal tract (GIT) and liver, and is usually associated with a poor outcome. We document a case of TAMA with exclusive GIT involvement which included the stomach, small and large bowel, presenting in a 66 year old male patient 5 years after complete resection of a type B2 thymoma. A brief review is provided of this scarce syndrome, the GIT pathology described in the 21 TAMA cases reported to date and the unique characteristics of patients with exclusive GIT involvement by this acquired autoimmune disorder.

Abstract

Thymoma-associated multiorgan autoimmunity (TAMA) is a recently delineated and rare paraneoplastic syndrome reported in patients with thymoma. The disorder is characterized by graft-versus-host disease (GvHD)-like pathology affecting the skin, gastrointestinal tract (GIT) and liver, and is usually associated with a poor outcome. We document a case of TAMA with exclusive GIT involvement which included the stomach, small and large bowel, presenting in a 66 year old male patient 5 years after complete resection of a type B2 thymoma. A brief review is provided of this scarce syndrome, the GIT pathology described in the 21 TAMA cases reported to date and the unique characteristics of patients with exclusive GIT involvement by this acquired autoimmune disorder.

Thymoma-associated multiorgan autoimmunity (TAMA) is a recently coined term for a rare paraneoplastic syndrome described in thymoma patients [1]. The syndrome is characterized by graft-versus-host disease (GvHD)-like pathology affecting the skin, gastrointestinal tract (GIT) and liver, with a total of 21 cases documented in the English literature to date [2 - 5]. We report a case of TAMA with exclusive GIT involvement, presenting 5 years after resection of a thymoma. A brief review of the literature on TAMA is also provided, with emphasis on the syndrome's GIT pathology, its histologic differential diagnoses and the unusual characteristics of patients with exclusive GIT involvement by this disorder.

Case report

A 66 year old Caucasian male presented to the gastroenterologist in June, 2014 with bloody diarrhoea of ten weeks duration. He was a known patient with Good syndrome (hypogammaglobulinemia) being followed up for type B2 (World Health Organisation classification) thymoma, resected with clear margins in February, 2009. There was no history of hematopoietic stem cell or other organ transplant, recent blood transfusion, prior auto-immune disease, skin lesions or liver function derangement. Work-up for the GIT symptoms, including stool microscopy, culture and PCR, and *Clostridium difficile* toxin testing, failed to identify an etiology. Antinuclear factor, coeliac disease and autoimmune gastritis serologies were negative. Antigoblet cell and antienterocyte serologies were unavailable.

Colonoscopy showed patchy inflammation and shallow ulcers throughout the colon (Fig 1). Large bowel biopsies revealed a pronounced apoptotic colonopathy with focal crypt distortion (Fig 2a). The lamina propria had a lymphocyte predominant increased cellularity. "Exploding crypt cells" and apoptotic crypt abscesses were noted (Fig 2b, c). Upper endoscopy was unremarkable, but biopsies revealed a mild chronic active gastritis with focal epithelial apoptosistic(Fig 2d, e - g). No *Helicobacter* spp. was detected on special and immunoperoxidase

Figure 1. Colonoscopic image showing patchy inflammation with multiple shallow ulcers

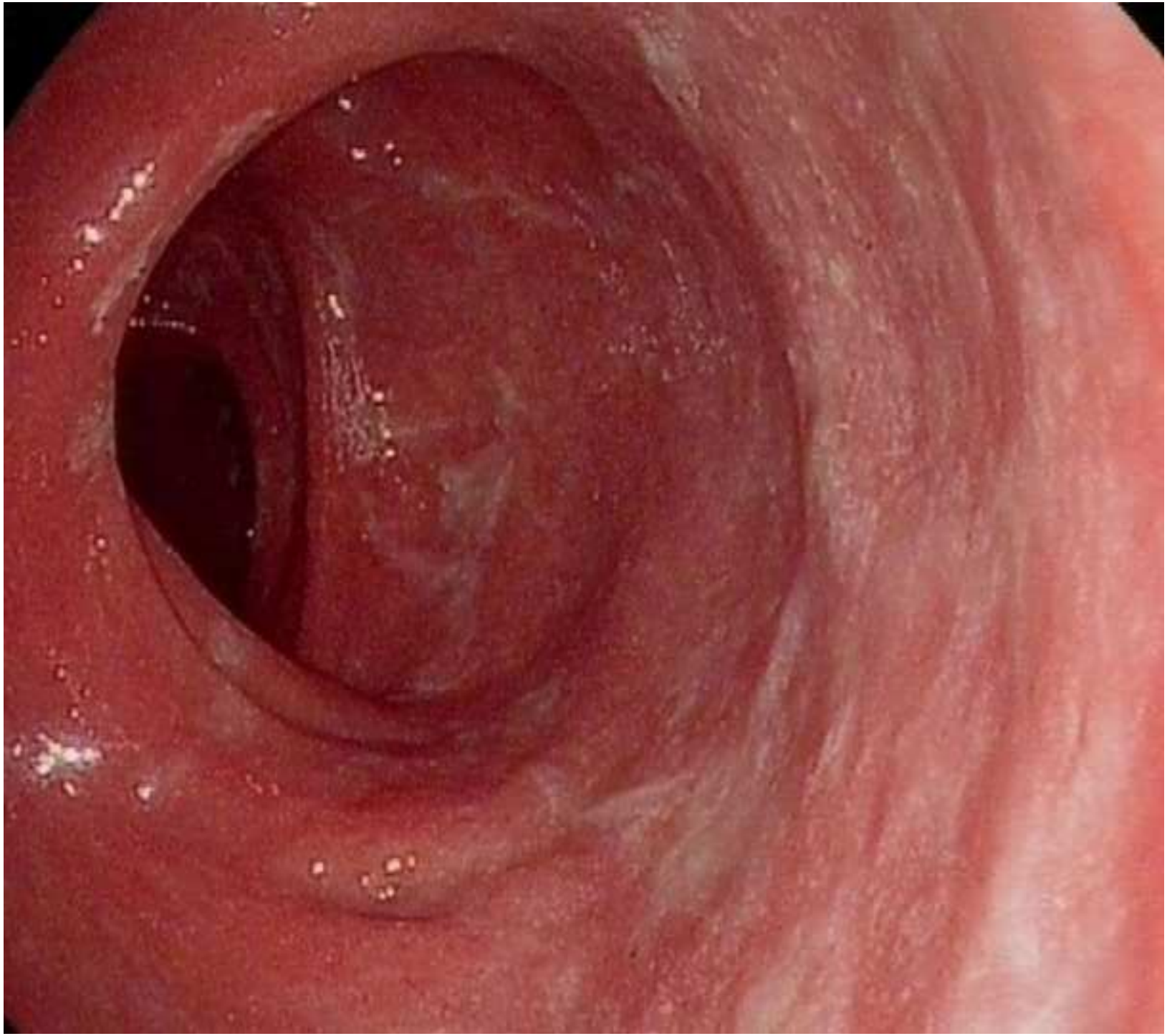


Figure 2. Colon biopsies illustrating apoptotic colonopathy with early crypt architectural distortion and lymphocyte-rich lamina propria (a, 100x). Pronounced crypt epithelial apoptosis (b, 400x), with associated apoptotic crypt abscess (c, 400x). Gastric biopsy with mild chronic active inflammation (d, 100x) and scattered apoptotic bodies (arrows, e, 400x). Duodenumdemonstrating villous blunting, inflammatory lamina propria expansion and loss of goblet cells (f, 100x), with associated epithelial apoptosis (g, 400x)

Figure 2b

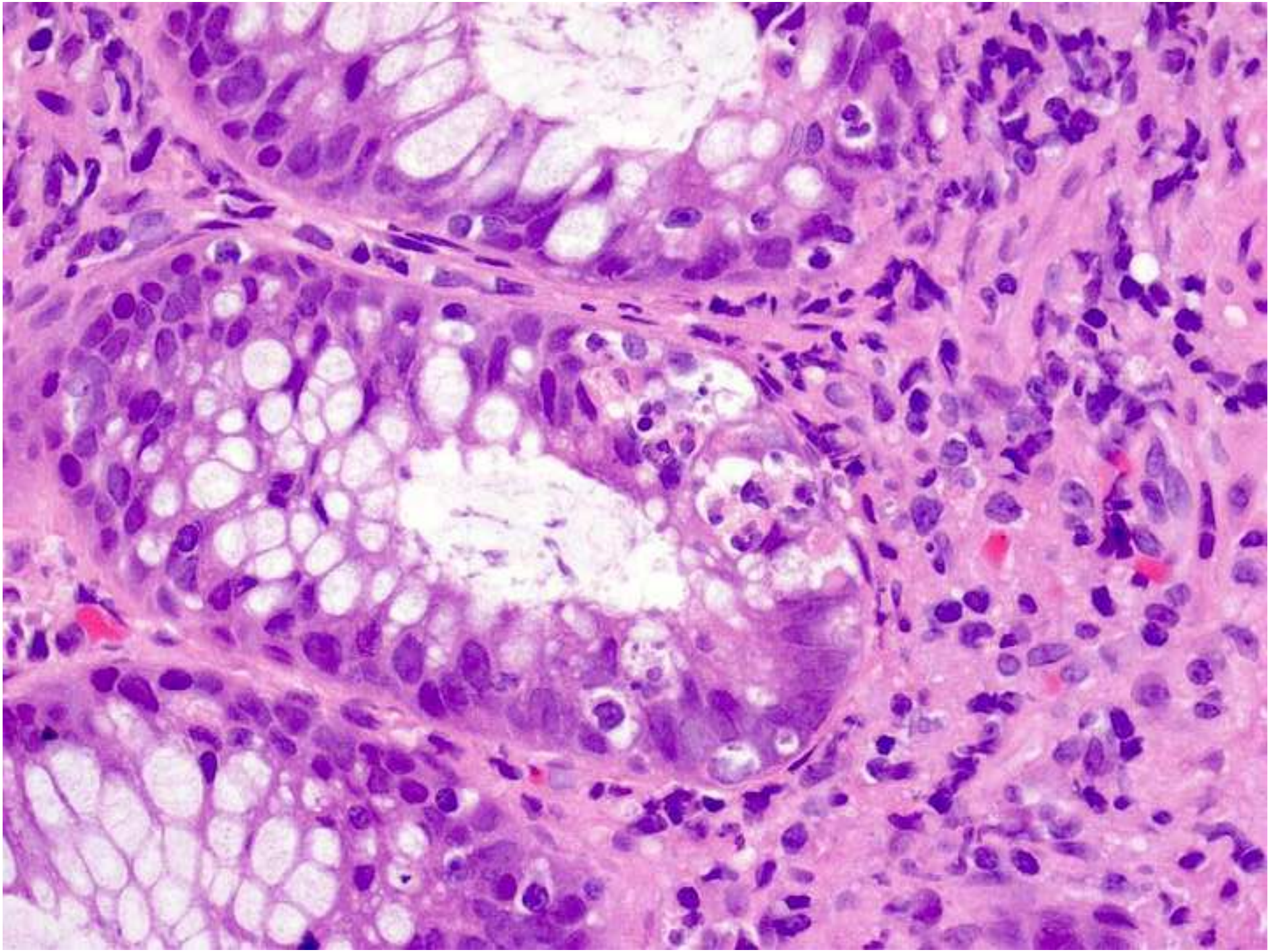


Figure 2c

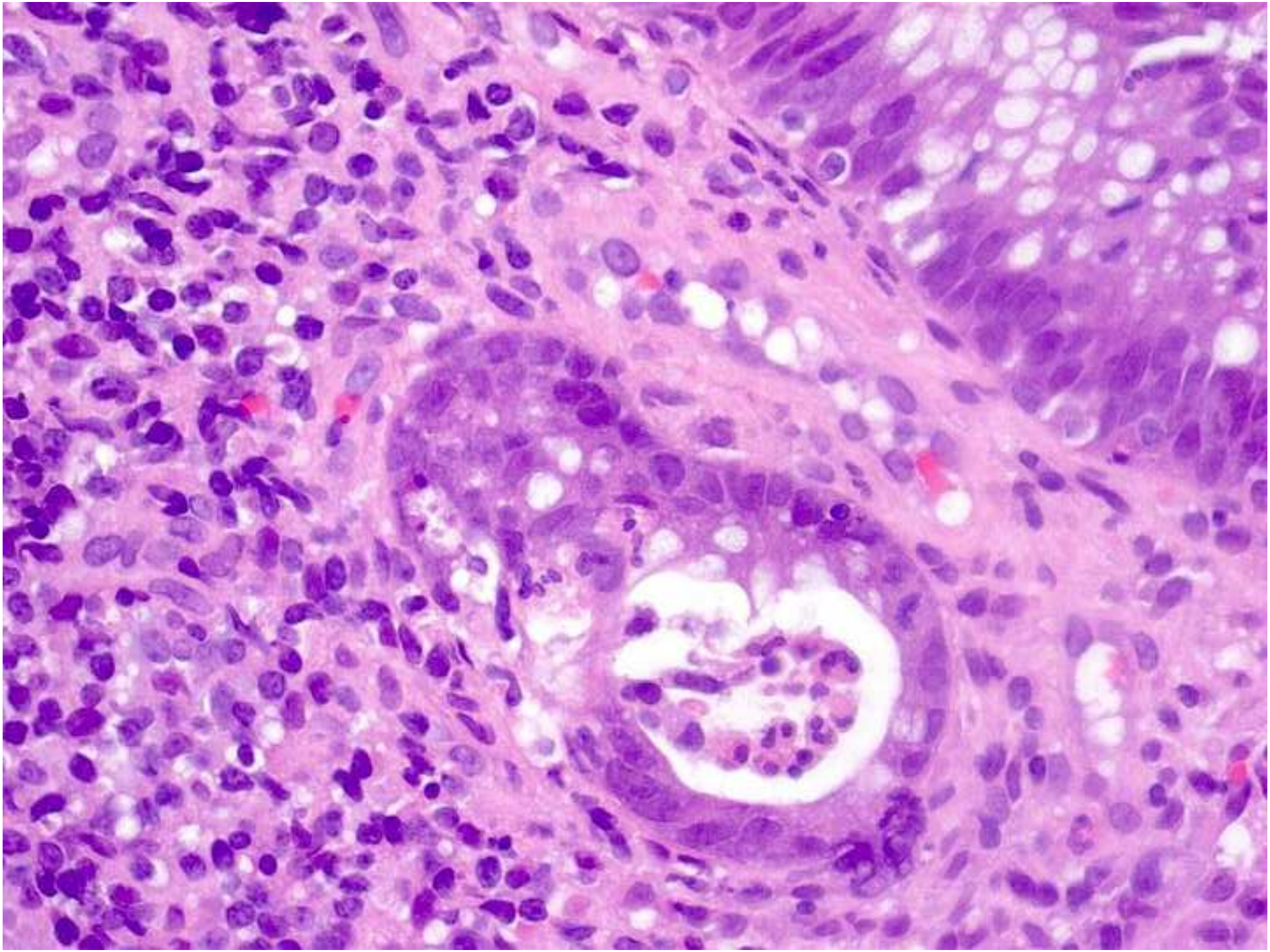


Figure 2d

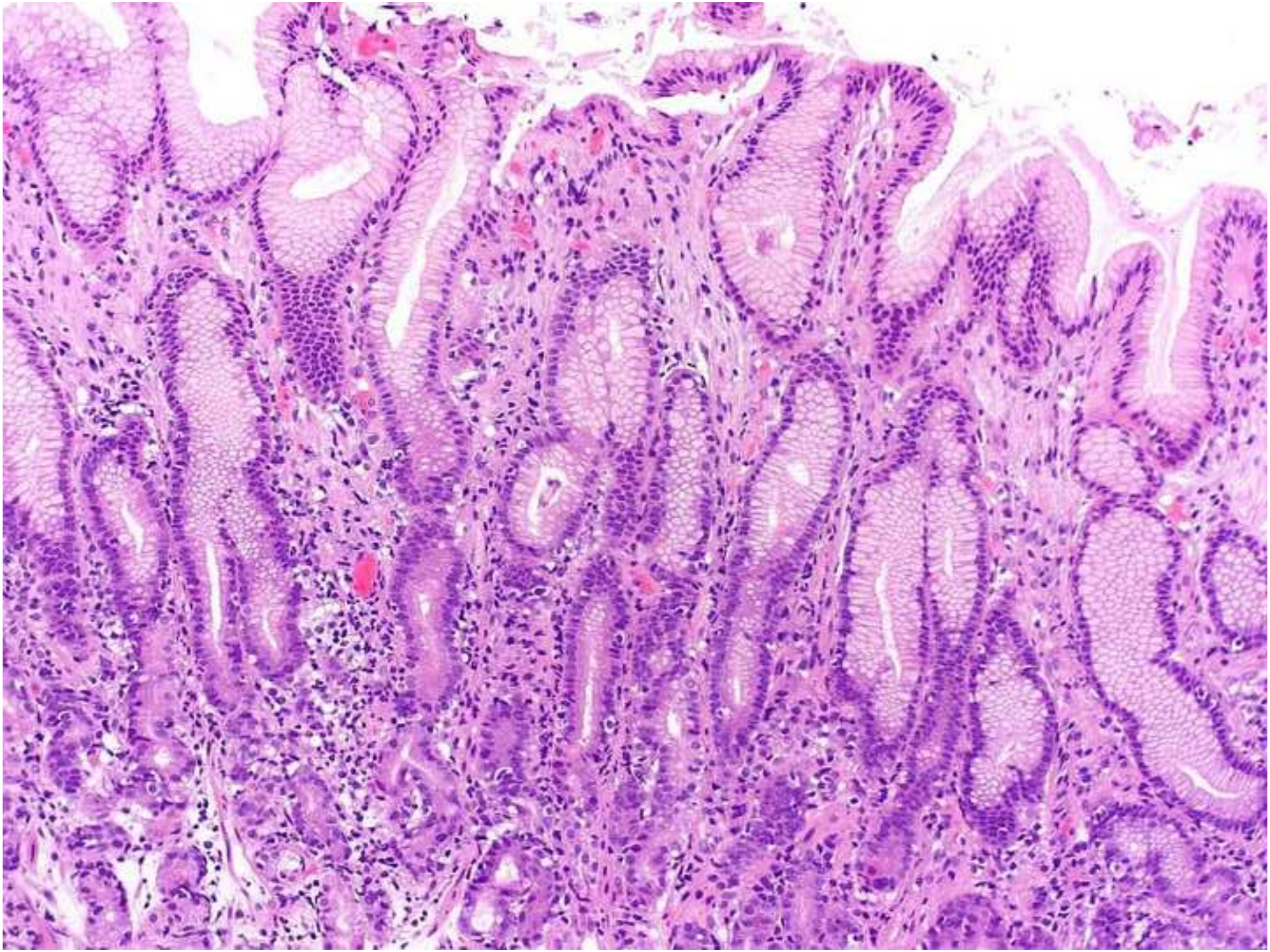


Figure 2e

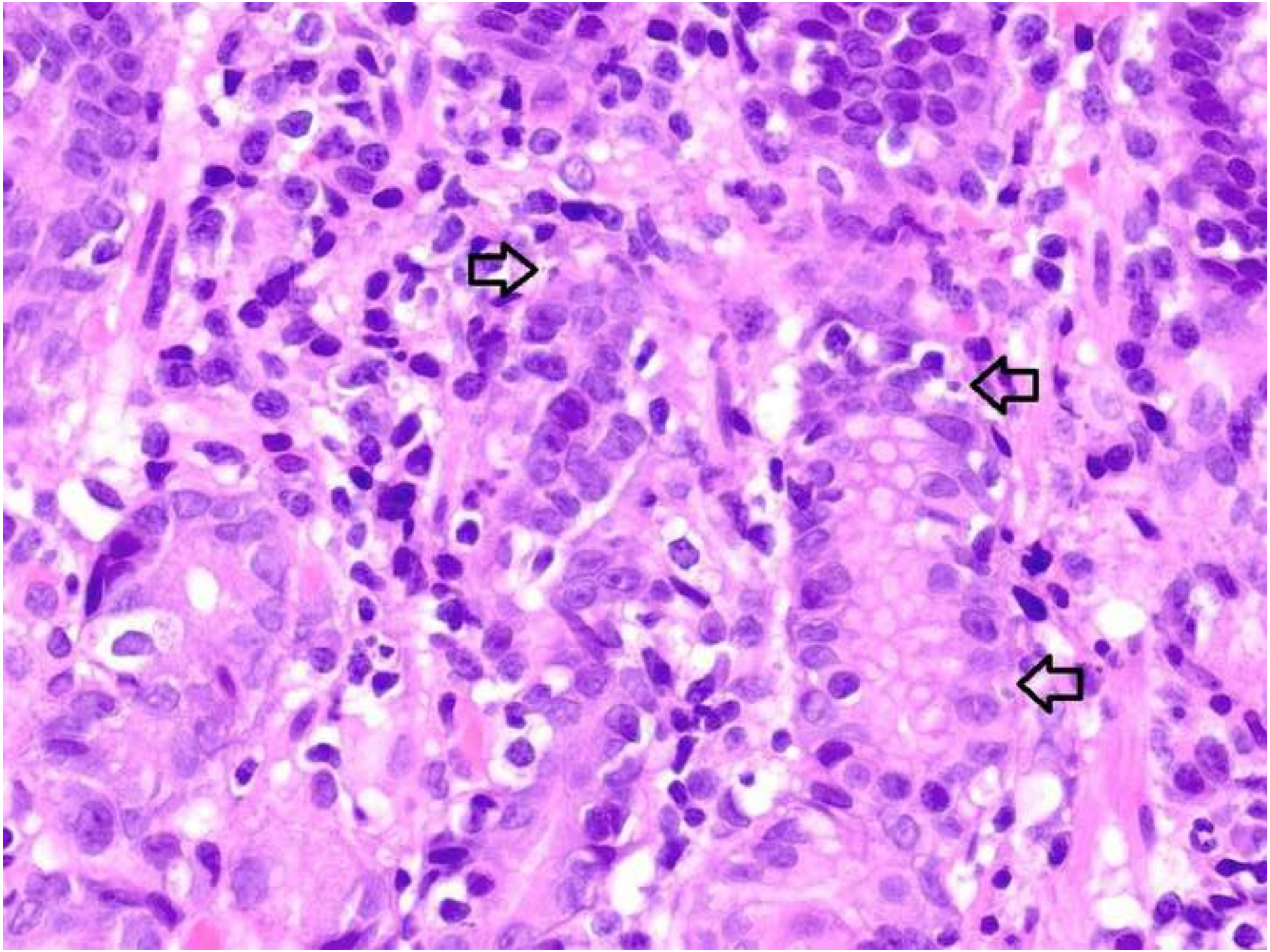


Figure 2f

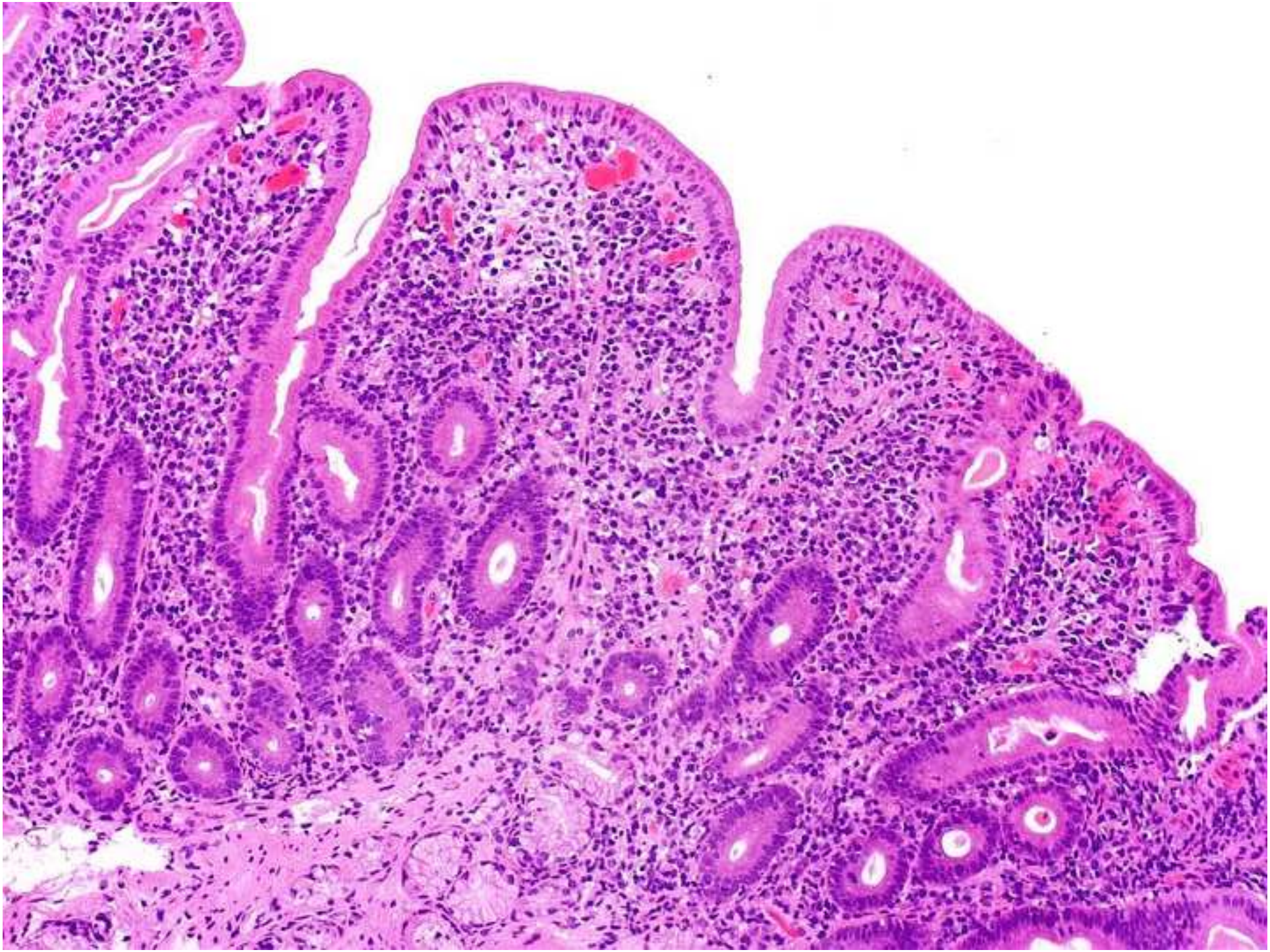
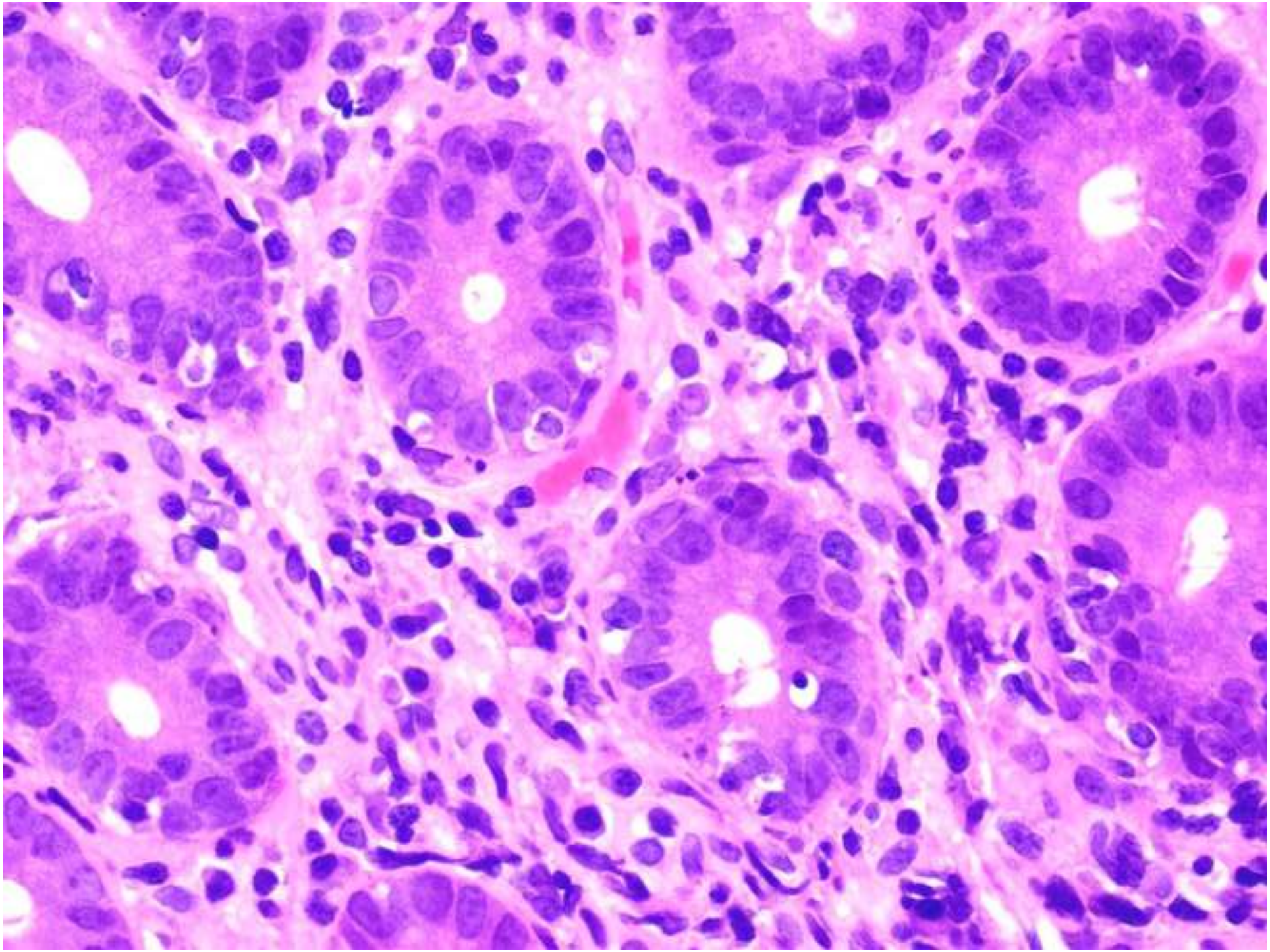


Figure 2g



stains. The duodenum showed villous blunting, lamina propria expansion by a predominantly lymphocytic infiltrate, prominent loss of goblet cells, Paneth cell paucity and epithelial apoptosis (Fig 2f, g). No viral inclusions were identified on routine, cytomegalovirus (CMV) and adenovirus immunoperoxidase stains. Meticulous medication history excluded drug-associated pathology.

A diagnosis of TAMA with exclusive GIT involvement showing predominant features of (GvHD-like enterocolitis) was rendered and azathioprine therapy commenced. The patient is currently alive and asymptomatic, 3 years and 9 months after initial diagnosis of his GIT pathology and 9 years post thymectomy, with no thymoma recurrence, skin or liver disease. He remains on monthly intravenous immunoglobulin supplementation for hypogammaglobulinemia and periodic azathioprine for flare-ups of his paraneoplastic autoimmune gastroenterocolonopathy.

Discussion

GIT involvement by GvHD-like colitis associated with thymic neoplasia was first documented by Kornacki et al in 1995 [2]. Subsequent reports described GvHD-like skin pathology and liver involvement afflicting patients with thymoma [6, 7]. In 2007, Wadhera et al proposed the term thymoma-associated multiorgan autoimmunity (TAMA) to encompass this enigmatic spectrum of pathology [1].

Although the pathogenesis remains incompletely understood, defective T-cell immune selection within the dysfunctional neoplastic epithelial environment of thymoma is favored [5]. Absent or decreased autoimmune regulator (AIRE) expression in neoplastic thymic epithelial cells may lead to incomplete deletion of self-reacting T-cells, which escape into the peripheral circulation and drive the GvHD-like pathology [4]. Decreased FOXP3 transcription factor expression and decreased numbers of regulatory T-cells also play a role [4, 8]. Whilst the resulting target organ changes may be histologically indistinguishable from GvHD, the absence of grafted lymphocytes necessitates the term “GvHD-like”. Genetic mutations in AIRE and FOXP3 are associated with childhood primary immunodeficiency and syndromic autoimmunity, further supporting the role of immune dysregulation in the pathogenesis of TAMA [9]. Not surprisingly, thymoma patients often have other associated autoimmune diseases such as myasthenia gravis, autoimmune thrombocytopenia, red cell aplasia and rheumatoid arthritis [4].

The 21 TAMA cases documented to date have shown a female predominance, with a mean age of 47 years at presentation [2 - 5]. Clinical features of paraneoplastic autoimmunity have manifested before, after or synchronously with the diagnosis of thymoma [10]. Most cases were associated with malignant or incompletely excised tumor, although complete thymoma removal does not preclude subsequent development of TAMA (as in our patient). Interestingly, eleven previous TAMA cases have manifested up to 18 years post thymoma

diagnosis / resection, and onset of autoimmune disease is not always associated with tumor recurrence [5]. Although the mechanism of this delayed disease onset is unclear, possible explanations include the role of memory T-cells, persistence of "thymoma educated" self-reactive T-cells with subclinical disease, and prolonged suppression of the self-aggressive T-cell population by "properly educated" regulatory T-cells, the inhibitory effect of which may be diminished by a subsequent immunological insult [4].

GIT symptoms and / or pathology were reported in 10 of the 21 TAMA patients [10]. Of these, one patient had chronic intractable diarrhea which was not investigated endoscopically and another patient was found to have esophageal candidiasis, without any other specific GIT microscopic pathology [1, 6]. Four of the remaining 8 patients had associated skin and / or liver involvement and demonstrated GvHD-like lower GIT pathology. Two of these cases also had concomitant GvHD-like duodenitis.

To date, only 5 TAMA patients (including our case) have shown exclusive GIT GvHD-like involvement [2 - 4]. Table 1 summarises the findings in this subgroup, which appears to show some differences to TAMA cases with associated skin and / or liver changes, or without documented GIT involvement. Exclusive GIT GvHD-like pathology has affected slightly younger patients (mean age at diagnosis = 43) and thus far occurred only in males. These 5 cases were associated with type B1, B2 or AB thymoma, all thymic neoplasms which contain a large number of non-neoplastic and immunologically impressionable T-lymphocytes. Previous patients revealed lower and upper GIT GvHD-like pathology, but the present case is the first to document microscopic gastric inflammatory involvement and histological evidence of colonic chronicity in TAMA.

A recent paper by Umetsu and colleagues has emphasized the diverse histologic features of autoimmune enteropathies (AIE), which can be divided into chronic active inflammatory, celiac disease-like, GvHD-like and mixed patterns [9]. To date, secondary autoimmune GIT pathology reported in TAMA has demonstrated GvHD-like features, although stomach and duodenal biopsies in this case revealed a mixed pattern. Involvement of numerous GIT sites, which may show discordant histologic patterns, is well documented in AIE [9].

TAMA patients who present with exclusive GIT GvHD-like involvement can pose a diagnostic challenge to the pathologist, particularly if there is no prior history of thymoma. Numerous causes of apoptotic gastroenterocolonopathy may enter the differential diagnosis. Reliable histologic distinction from GvHD in the setting of a hematopoietic stem cell or (less often) solid organ transplant is impossible without an appropriate history. A myriad of drugs may be associated with GIT GvHD-like changes. Mycophenolate / mycophenolic acid typically shows a patchy paucicellular lamina propria, cystic crypt dilation and numerous eosinophils, microscopic features which assist in diagnosis [11]. Other offending drugs include anti-neoplastic agents such as 5-fluorouracil, cyclosporine A, non-steroidal anti-inflammatory drugs and newer immune modulators such as PD-1 inhibitors [12, 13]. GIT viral infections, particularly cytomegalovirus (CMV) and adenovirus, may lead to prominent epithelial apoptosis but detection of characteristic cellular inclusions will confirm this diagnosis.

Table 1 . Findings in TAMA patients with exclusive GIT GvHD-like pathology [2 – 4]

Case	Age (years)	Sex	GIT symptoms	Endoscopic findings	Lower GIT pathology	Upper GIT pathology	Thymoma type (WHO)	Other clinical findings	Reference
1	20	M	Episodic watery diarrhea	Patchy colonic erythema, edema	GvHD-like ileocolitis	GvHD-like duodenitis	B2	-	Kornacki et al
2	46	M	Severe chronic diarrhea	NS	GvHD-like colitis	NS	B1	-	Sader et al
3	20	M	Diarrhea	NS	GvHD-like colitis	GvHD-like duodenitis	B1	AIT	Offerhaus et al
4	61	M	NS	NS	GvHD-like colitis	GvHD-like duodenitis	AB	RA	Offerhaus et al
Our case	66	M	Chronic bloody diarrhea	Patchy colitis with ulceration	GvHD-like colitis	Gastro-duodenitis (mixed pattern)	B2	HG	-

NS, not specified; AIT, autoimmune thrombocytopenia; RA, rheumatoid arthritis; HG, hypogammaglobulinemia

Congenital immune deficiencies such as combined variable immunodeficiency (CVID), and acquired immune disorders including combined variable immunodeficiency (CVID), various acquired autoimmune diseases anprimary AIE of adults and HIV infection can mimic the GvHD-like GIT pathology of TAMA [9, 11, 14]. Lymphoid hyperplasia and a paucity of plasma cells in CVID, and the presence of other histologic patterns in the rare cases of primary adult-onset AIE are histologic a clues. A specific diagnosis, however, necessitates close clinical correlation. Other disorders such as acute ischemia, radiation and chronic inflammatory bowel disease may be associated with prominent GIT epithelial apoptosis, but characteristic microscopic features of the underlying pathology usually make the primary diagnosis apparent [11].

Manifestations of paraneoplastic autoimmunity are usually more severe, more difficult to treat and show a broader clinical spectrum than autoimmune disease unassociated with neoplasia [15]. Accordingly, the overall survival in TAMA patients is poor with a mortality of approximately 70% within 4.5 years post syndrome diagnosis [5]. TAMA patients frequently succumb to infective complications secondary to immune suppression required to treat the paraneoplastic syndrome or chemotherapy administered for thymoma control [5].
Interestingly, exclusive GIT involvement in TAMA seems to be associated with a better overall outcome. The patients in this subgroup were all alive at the time of the respective manuscript submission, follow-up ranging from months to 3 years and 9 months post TAMA diagnosis and up to 17 years post thymoma resection [2 - 4].

Conclusion

TAMA is an extremely rare GvHD-like paraneoplastic disorder, which uncommonly presents with exclusive GIT involvement. The latter subgroup, characterized by a GvHD-like secondary autoimmune enterocolonopathy, appears to have somewhat different clinical features to TAMA patients reported to date. and may present a particular diagnostic challenge to the pathologist and lead to consideration of numerous other histological differential diagnoses. Careful correlation with relevant history, clinical findings (especially pertaining to previous thymoma, current mediastinal mass, prior transplantation and drug administration) and diligent evaluation of endoscopic biopsy material will aid the pathologist in clinching the is unique diagnosis of this enigmatic paraneoplastic autoimmune GIT pathology.

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