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Complications Related to the Late Diagnosis of Coeliac Disease

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Abstract

Background: Coeliac disease (CD) can lead to complications such as adenocarcinoma of the small bowel, lymphomas and refractory coeliac disease (RCD).

Observations: The incidence of such diseases is higher in patients with CD who have a prolonged exposure to gluten and/or non-compliance with a gluten free diet. Here we present four cases of complicated CD namely adenocarcinoma of the small bowel, T cell lymphoma and RCD.

Conclusions: This highlights the importance of diagnosing CD early and the need for long term follow-up in clinic.

Keywords

coeliac disease; refractory coeliac disease; adenocarcinoma; T cell lymphoma

Abbreviations

Coeliac Disease; RCD: Refractory Coeliac Disease; GFD: Gluten-free diet; CT: Computed Tomography; Anti-TTg-IgA: anti-tissue transgultaminase antibody; EATL: enteropathy-associated T-cell lymphoma; UJI: ulcerative jejunoileitis

Background

Coeliac disease (CD) is a chronic immune-mediated small intestinal enteropathy that is triggered by exposure to dietary gluten in genetically predisposed individuals [1]. The incidence of CD in western countries is about 1% [2]. Patients typically report signs and symptoms suggestive of malabsorption such as chronic persistent diarrhoea, steatorrhea, weight loss, abdominal bloating after meals or failure to thrive. Non-classical presentations of CD include depression, osteoporosis, elevated liver enzymes, anaemia or following screening of asymptomatic relatives of patients with CD [3,4]. IgA anti-tissue transglutaminase antibody (Anti-TTg-IgA) has a sensitivity and specificity of about 95% for CD and is recommended as the preferred first test for detection of CD in individuals over the age of 2 [3]. Endomysial antibody is also elevated. Diagnosis of CD, however, requires a duodenal biopsy showing typical histology such as increased intraepithelial lymphocytes, villous atrophy and crypt hyperplasia whilst the patient is on a diet containing gluten [4]. These changes can be classified according to the modified Marsh classification (Table 1) [5]. The mainstay of treatment is a gluten-free diet (GFD), which entails avoidance of products containing the proteins from wheat, barley and rye [4].

Coeliac-related malignancies and disorders that mimic CD should be excluded in symptomatic patients with ongoing enteropathy. In patients with symptoms of persisting abdominal pain, fever,

obstruction, anaemia, gastrointestinal bleeding or unexplained weight loss, small bowel imaging and repeat duodenal biopsy should be strongly considered [4].

There are several complications associated with CD which include refractory coeliac disease (RCD), enteropathy-associated T-cell lymphoma (EATL), abdominal B-cell lymphoma, small intestinal adenocarcinoma and ulcerative jejunoileitis (UJI) [3,4,6,7]. Various studies have shown that the main risk factor for CD complications is poor compliance with a GFD, with the risk being more relevant for the intestine-specific malignancies and non-Hodgkin's lymphoma [8,9,10]. Other important factors are the diagnostic delay of CD, age at diagnosis and homozygozity for HLA-DQ2 [9,10,11].

Case 1

A 32-year-old male was admitted with a one and a half month history of diarrhoea up to 16 motions per day and weight loss of 9kg over the same time frame. He also reported colicky abdominal pain, nausea and decreased appetite. He had previously been healthy and did not smoke. On examination he was cachectic and pale with minimal periumbilical tenderness on palpation of the abdomen. Anti-TTg-IgA level was 200 u/ml (0-10u/mL). Bloods showed a low albumin level of 26.8 g/l (35-55g/L). A computed tomography (Ct) of the abdomen was reported as normal. Duodenal biopsies demonstrated increased intraepithelial lymphocytes, crypt hyperplasia and subtotal villous atrophy which are consistent with a histological diagnosis of CD (Marsh 3b) (Figure 1).

Two months later he was readmitted with worsening diarrhoea and weight loss of 10kg despite a GFD. He reported vomiting, generalized weakness, lethargy and fever. A repeat gastroscopy confirmed the previous findings (Figure 2). Stool samples were negative for infections. Faecal elastase levels were low indicating pancreatic insufficiency. His serum albumin had dropped to 16.8g/dl. Anti-goblet cell antibodies were negative. A Ct scan demonstrated multiple small lymph nodes aggregated around the root of the mesentery, distended small and large bowel, bilateral pneumonias, a 1.7cm pericardial effusion (confirmed with echocardiography), pulmonary artery thrombosis and ascites (Figure 3). During colonoscopy few apthous ulcers throughout the colon were noted. Histology from the terminal ileum demonstrated pronounced diffuse lymphocytic infiltrate intermixed with lymphoid follicles. Lymphocytes were entirely CD20 positive B-cells with intermixed CD4 and CD8 positive T lymphocytes. These findings were consistent with atrophic enteropathy (coeliac disease). Biopsies from the apthous ulcers demonstrated focal active colitis. Capsule endoscopy revealed similar ulcers in the small bowel and atrophic mucosa (Figure 4).

A provisional diagnosis of RCD type 1 was made and he was started on intravenous hydrocortisone. He developed bleeding per rectum and high fever despite antibiotics and transferred to intensive care unit due to haemodynamic instability. He was given parental nutrition, elemental diet and supplementary pancreatic enzymes. Ct showed extensive lung consolidations, ascites and small bowel and large bowel lumina that were distended with fluid. Echocardiography displayed a moderate pericardial effusion not causing tamponade with a restrictive cardiomyopathy. His renal function deteriorated leading to the need for dialysis. He developed respiratory failure requiring intubation. Despite maximal supportive care in the intensive care unit, disseminated intravascular coagulation ensued and he passed away secondary to multi-organ failure four months after the initial presentation.

Case 2

A 70-year-old female presented with a 20-year history of diarrhoea which recently got worse. On examination she was noted to have severe lower limb oedema. Blood investigations were normal except for a high Anti-TTg-IgA (> 100U/ml) and a positive anti-endomysial antibody. At endoscopy the features in her duodenum were suggestive of CD. Duodenal biopsies confirmed CD Marsh 3a, indicating increased intraepithelial lymphocytes, crypt hyperplasia and partial villous atrophy. Ct scan of the abdomen was performed and it was normal. She was started on a GFD and was compliant.

Four weeks later she complained of increasing lethargy and worsening diarrhoea despite a GFD. She reported abdominal pain and occasional blood per rectum. On examination, she was noted to have epigastric tenderness and lower limb oedema. Blood investigations revealed a raised total white cell count of 18.40x10^9/L (4.00-11.0 x 10^9/L) which were mostly neutrophils at 16.16 x10^9/L (2.5–7.5 x 10^9/L), anaemia (Haemoglobin 11.5 g/dl; range 14.0-17.5 g/dL), thrombocytosis (platelets - 618 x10^9/L ; range 150- 450,000 x10^9/L), hypoalbuminaemia (albumin - 26.0g/l range 35-55g/L) and a raised anti-TTg-IgA level (>100u/ml). A repeat Ct scan showed bilateral pleural effusions, ascites, generalized subcutaneous oedema, mesenteric oedema and air and fluid within the abdominal cavity. Laparotomy was performed in view of suspected bowel perforation. During the procedure 3 different jejunal perforations were identified and 1.2L of bile-tinged purulent fluid was aspirated. A 40cm resection of the small bowel was done and a stoma was fashioned. The histology showed a dense infiltrate of atypical large lymphoid cells involving the entire thickness of the small bowel and the mesentery. The neoplastic cells showed expression of CD3 and CD30, consistent with high grade intestinal T cell lymphoma (Figures 5 and 6).

The post-operative period was complicated by sepsis, for which supportive care was given. Magnetic Resonance Imaging of the brain and analysis of cerebrospinal fluid samples obtained from a lumbar puncture were normal. Repeat Ct showed bilateral pleural effusions and consolidations in both lungs. There was no abdominal pathology apart from gross oedema of the abdominal wall. She passed away one week after the laparotomy in the intensive care unit.

Case 3

A 38-year-old female was admitted to hospital with a 3-month history of lower back pain, vomiting and lethargy. On examination, a mass was palpable in the left upper quadrant. Blood tests showed anaemia of 7.9 g/dL (11.5-15.5g/dL) with a low ferritin level and thromobocytosis (platelets - 496 range 150- 450,000 x10^9/L). Ct demonstrated irregular thickening of the proximal jejunum with ulceration, lymphadenopathy and liver metastases (Figure 7). Anti-TTG-IgA levels were elevated at 96.2 U/ml and the anti-endomysial antibodies were positive as well. A laparotomy was performed and a small bowel tumour was identified 10cm from duodenojejunal flexure invading the mesentery. Since it could not be resected, agastrojejunostomy and a jejunojejunostomy were performed in view of impending obstruction. Liver metastases were noted in the both hepatic lobes. Histology confirmed intestinal type adenocarcinoma as indicated by the fact that the tumour expressed CK20 and CDX2 and was negative for CK7, EMA, synaptophysin and Chromogranin-A (Figure 8). She was given 5 cycles of Folfox chemotherapy (Leucovorin Calcium, Fluorouracil, Oxaliplatin) and repeat Ct showed that the jejunal mass decreased by half its size when compared to the previous scan, with decrease in size of the lymphadenopathy. After

cycle 7, she underwent hepatic metastectomy and resection of the small bowel tumour which was staged as pT4bN2bM1a. She was given a further 4 cycles of Folfox. Repeat Ct and Positron emission tomography scan showed progression of the disease with extensive involvement of the nodes in the mediastinum and abdomen with left hydronephrosis due to compression on the left urether by lymphadenopathy. She was given 12 cycles of Folfiri chemotherapy (Leucovorin Calcium, Fluorouracil, Irinotecan Hydrochloride) and required Granulocyte colony-stimulating factor due to neutropaenia. A left nephrostomy was inserted as stenting of the left urether could not be done due to the severity of the stricture. She was restarted on palliative Folfiri due to severe pain as a result of progression of the disease that was evident on CT. The patient passed away 28 months post-diagnosis, secondary to her metastatic disease.

Case 4

A 48-year-old female was admitted with a 2 month history of worsening abdominal distension, change in bowel habits, loss of appetite and lower back pain. She denied nausea, vomiting or fever. She had a history of an uncomplicated appendectomy in childhood and had a 30 pack year history of cigarette smoking. On examination she was cachectic and dehydrated and on palpation her abdomen was soft but distended. A Ct scan demonstrated small bowel obstruction with mesenteric root volvulus (Figure 9). Laparotomy was done and a small bowel obstructing tumour was identified with about 10cm of bowel constriction proximally. 20cm of small bowel were resected and a side-to-side anastomosis was done. Histology confirmed a circumferential moderately differentiated adenocarcinoma (Figure 10) with the tumour infiltrating and breaching the visceral serosa. Extensive peritumoural angiolymphatic invasion was seen. The resection margins were clear and there were no affected lymph nodes. In view of the association of small bowel adenocarcinoma and CD a gastroscopy was performed and this confirmed CD (Marsh 3B). She was started on a GFD and was given 12 cycles of Folfox chemotherapy due to T4 stage disease. She proceeded to have a good recovery and 36 months later she is in remission and has normal coeliac serology.

Discussion

Complications associated with CD include refractory coeliac disease (RCD), enteropathy-associated T-cell lymphoma (EATL), abdominal B-cell lymphoma, small intestinal adenocarcinoma and ulcerative jejunoileitis (UJI) [4,6,7]. Overall risk of malignancy associated with CD varies between 11% and 18.6% [6].

RCD is defined as persistent or recurrent malabsorptive symptoms and/or signs with villous atrophy despite a strict GFD for more than twelve months [1]. RCD affects 1-2% of patients with CD [2,12] and can be subdivided into two subtypes; RCD I and II. In RCD I, the immunophenotype of the intraepithelial lymphocytes is normal or polyclonal whilst in RCD II they are abnormal or monocolonal [6,13,14]. Patients with RCD II have a poorer prognosis [10] mainly due to nutritional complications, transformation into EATL and formation of UJI [10,14]. Studies have shown an overall 5-year survival of 93-96% in patients with RCD I. On the other hand, this dropped to 40-58% in patients with RCD II and 8% with the development of EATL in RCD II [13,14,15]. Other causes of death in RCD II include lymphoma, malnutrition and sepsis [3,15]. Treatment for RCD I includes elemental diet, systemic steroids, enteric coated oral budesonide and azathioprine [4,14,16]. There is no effective treatment for RCD II, however systemic steroids, cyclosporine and cladribine have been used. Use of high-dose chemotherapy followed

by autologous hematopoietic stem cell transplantation has been explored. Improvement with biological therapy such as infliximab and alemtuzumab for both RCD I and II have been reported. Surveillance for EATL in RCD II is also of paramount importance [3,4,14,15] RCD I was diagnosed in our first patient. RCD II was excluded due to the presence of intraepithelial lymphocytes that were morphologically normal and expressed CD4 and CD8.

The second patient had mucosa-associated T cell lymphoma, supported by a dense infiltrate of atypical large lymphoid cells expressing CD3 and CD30. EATL arises due to clonal expansion of neoplastic T-cell clones and can develop in either patients with RCD II (secondary EATL) or without a previous history of complicated CD (primary or de novo EATL) [14,15]. The prognosis of EATL is poor, with a 5 year survival rate of 11-20%. Treatment for EATL is chemotherapy (cyclophosphamide, doxorubicine, vincristine and prednisone: CHOP), with autologous stem cell transplantation and/or surgery depending on the case [15].

EATL, however, is not the most prevalent type of lymphoma in CD. A variety of other lymphomas have been associated with CD and these include primary gastrointestinal B cell and T cell lymphomas and malignant lymphomas outside of the gastrointestinal tract [17].

CD is also associated with increased risks of other malignancies such as small-intestinal, colon, oesophageal and gastric carcinomas. Small bowel adenocarcinoma is the second most common invasive malignancy after lymphoma [10]. A study in 2003 found that 13% of patients with small bowel adenocarcinoma also had CD [18]. This might suggest that patients with newly diagnosed small bowel adenocarcinoma should be screened for CD. Surgery may offer a curative resection rate of 40–65% [19]. Two of our discussed patients had small bowel adenocarcinoma.

Our first patient exhibited small bowel atrophy. He also exhibited aphthous ulcers (histology focal active colitis) throughout the small and large bowel. Histology showed focal active colitis. Persistent gluten exposure and small bowel bacterial overgrowth may lead to apthous ulceration and focal active colitis [20].

Conclusions

These cases highlight the importance of making an early diagnosis of CD and the need for long term follow-up. When symptoms persist despite compliance to a GFD, further investigations should be carried out to diagnose complications.

Table

Marsh Type	IEL / 100 enterocytes – jejunum	IEL / 100 enterocytes - duodenum	Crypt hyperplasia	Villi
0	<40	<30	Normal	Normal
1	>40	>30	Normal	Normal
2	>40	>30	Increased	Normal
3a	>40	>30	Increased	Mild atrophy
3b	>40	>30	Increased	Marked atrophy
3c	>40	>30	Increased	Complete atrophy

Figures

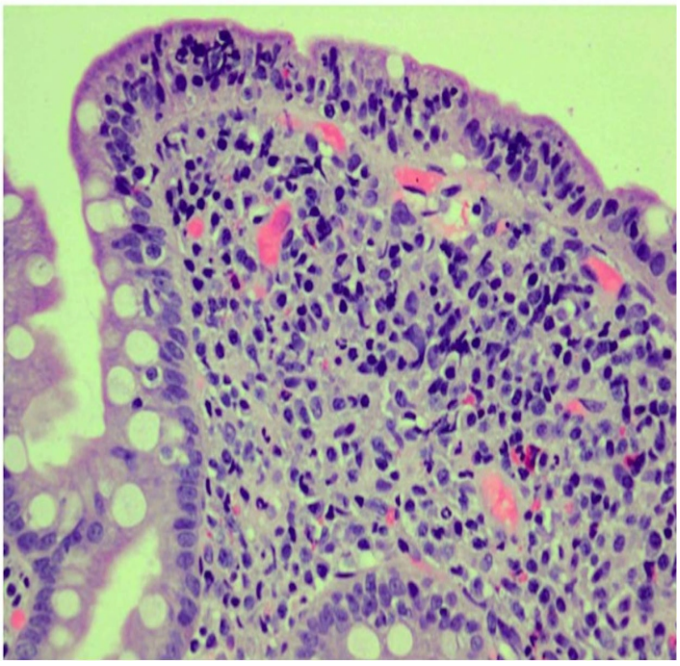

Figure 1: The photomicrograph shows broad-based and stunted duodenal villi with an increased intraepithelial lymphocytic infiltrate amounting to more than 25 lymphocytes per 100 enterocytes. Also noted is an increased lymphoplasmacytic infiltrate in the lamina propria.

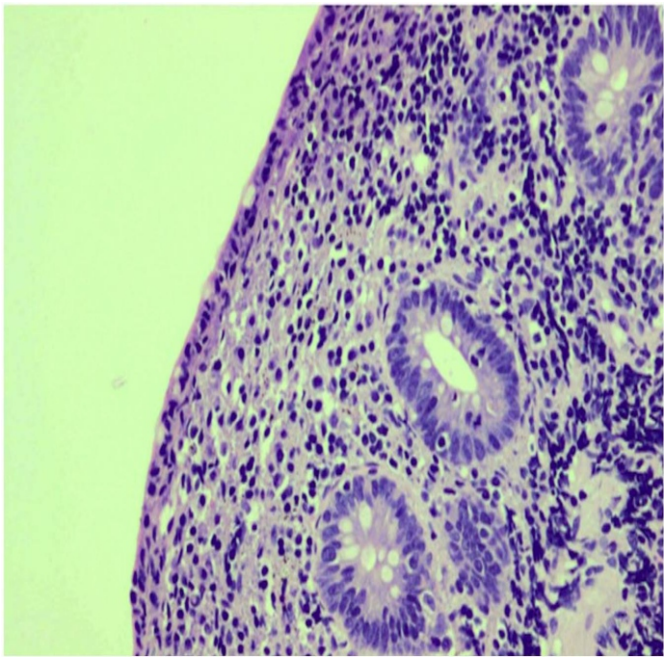

Figure 2: The photomicrograph shows flattened and atrophic villi with an increased intraepithelial lymphocytic infiltrate in both superficial and crypt epithelium together with an increased lymphoplasmacytic infiltrate in the lamina propria.

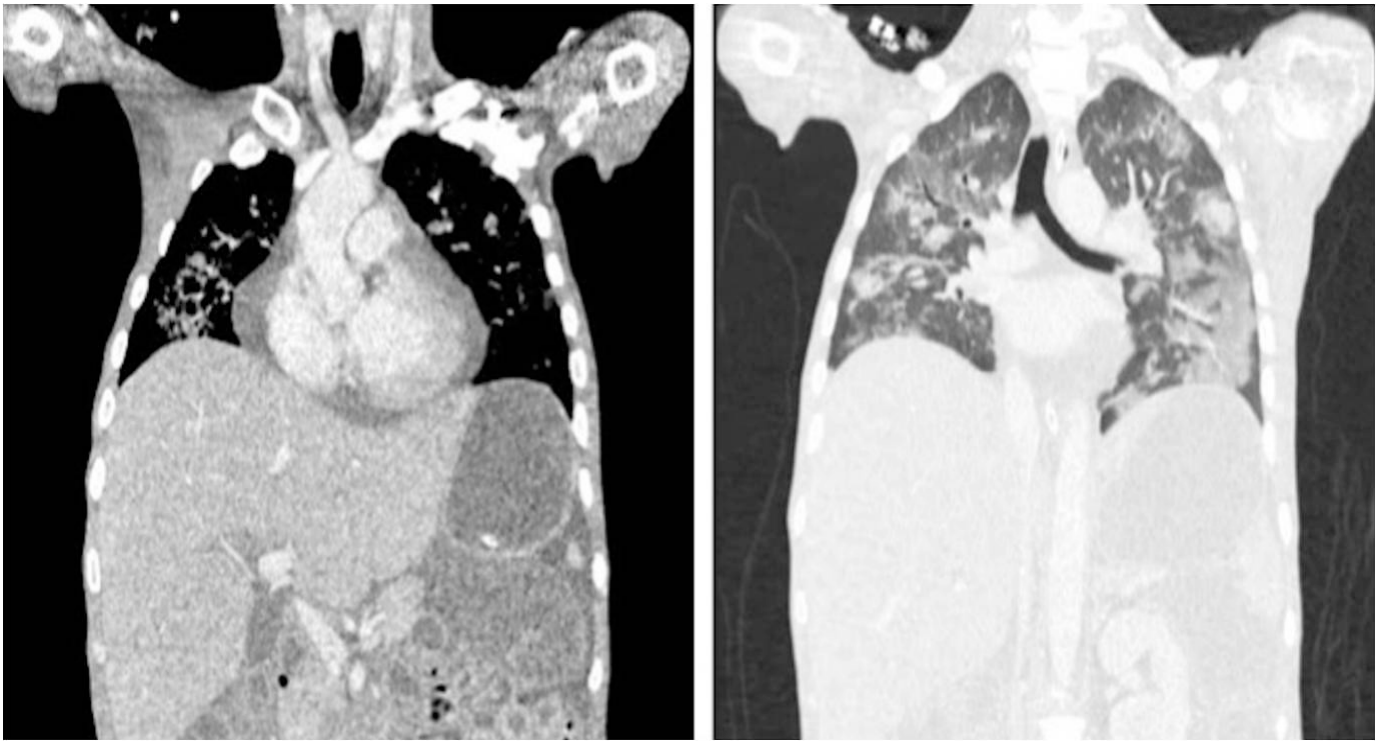

Figure 3: Coronal image in (a) abdominal and (b) lung window setting, demonstrates a pericardial effusion, bilateral patchy areas of ground-glass change in the lungs and ascites.

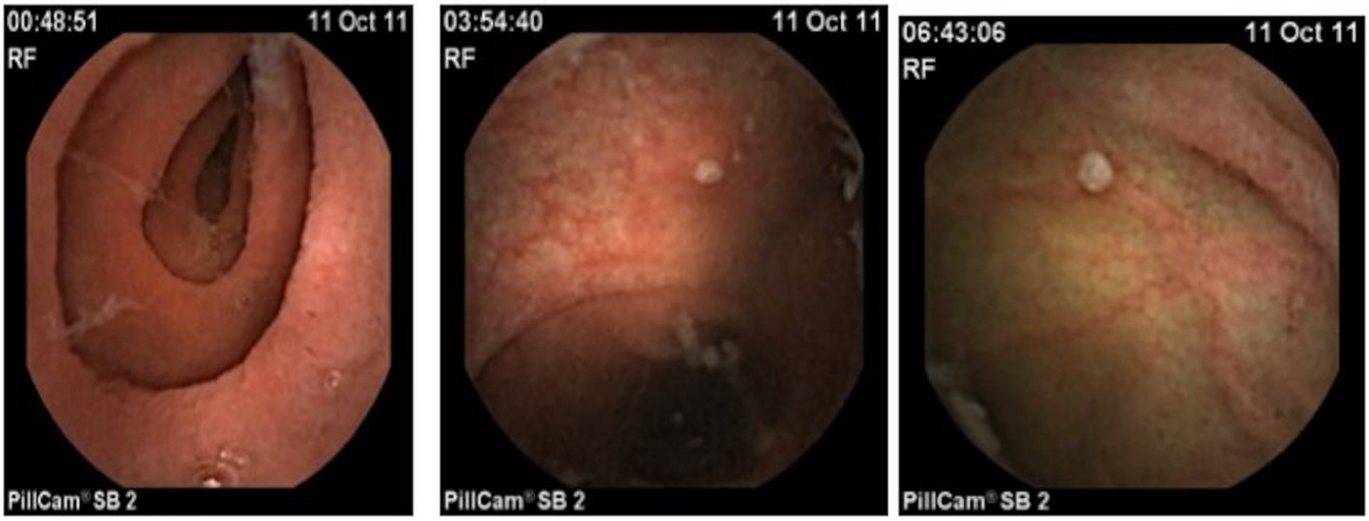

Figure 4: (a) Capsule endoscopy images showing atrophy and scalloping of mucosa; (b & c) Ulcerations in the small bowel

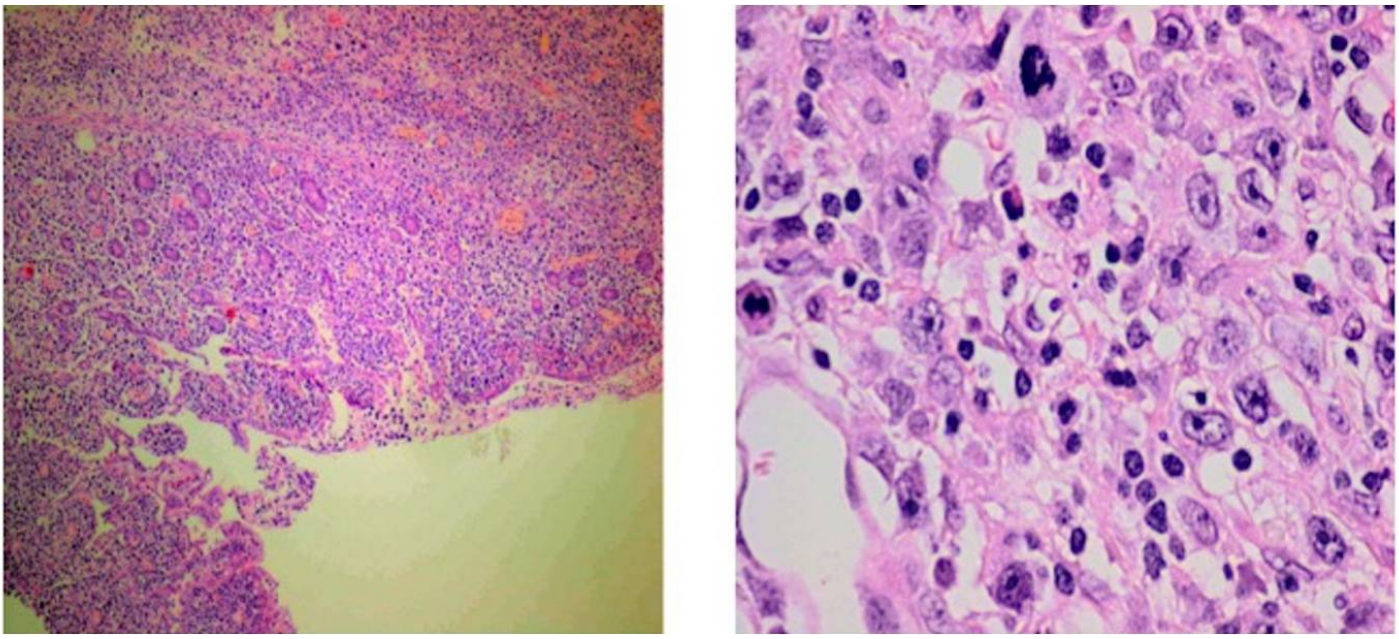

Figure 5: (a) x40 The photomicrograph shows broad-based and stunted duodenal villi and crypt hyperplasia with dense infiltrate of lymphoid cells. (b) x400 The lymphoid infiltrate is composed of medium sized to large atypical cells with irregular or oval shaped nuclear contours and prominent nucleoli. Mitotic figures are readily identified

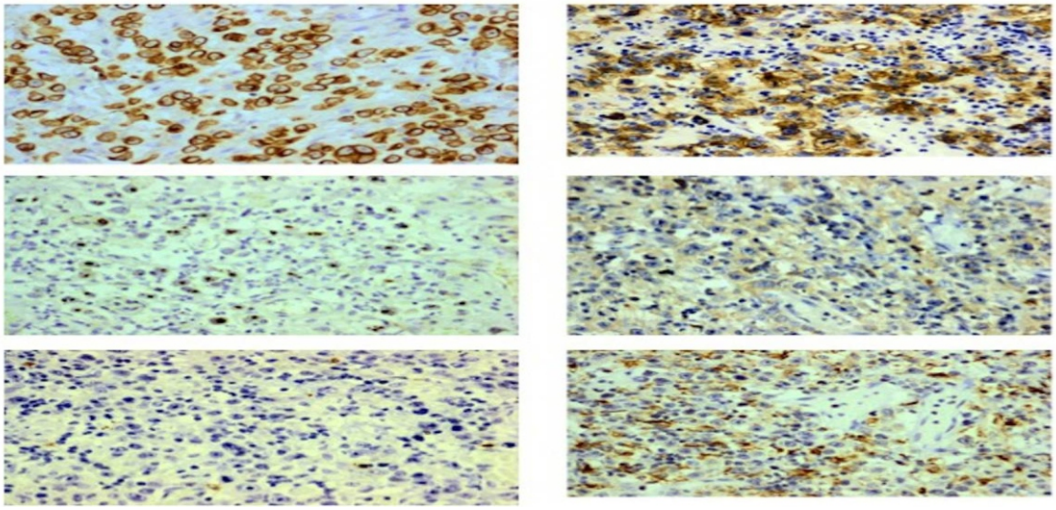

Figure 6: x200 The atypical lymphoid cells express (a) CD3 and (b) CD30. They do not express (c) CD20, (d) CD4, (e) CD8, or (f) CD68

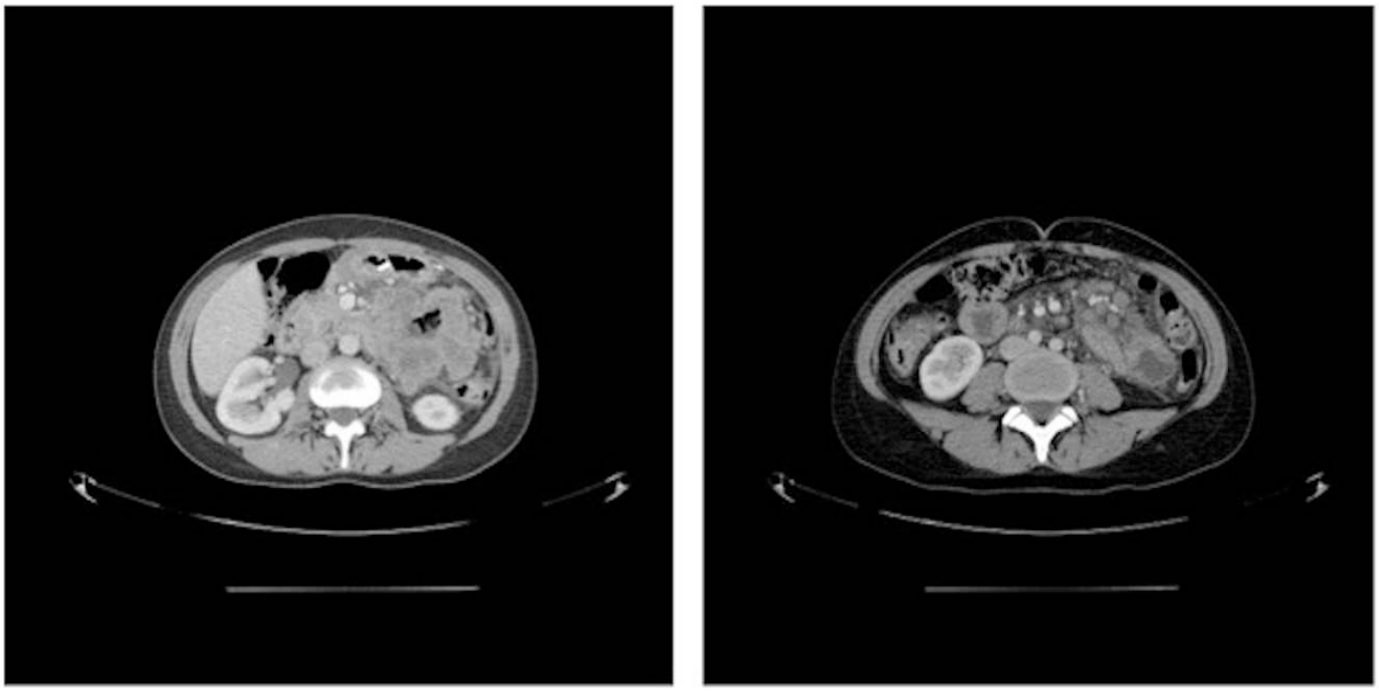

Figure 7: Lymphoma involving the proximal jejenum. (a) CT image demonstrates irregular mural thickening of the proximal jejenum. (b) CT image in the same patient demonstrates multiple enlarged mesenteric lymph nodes.

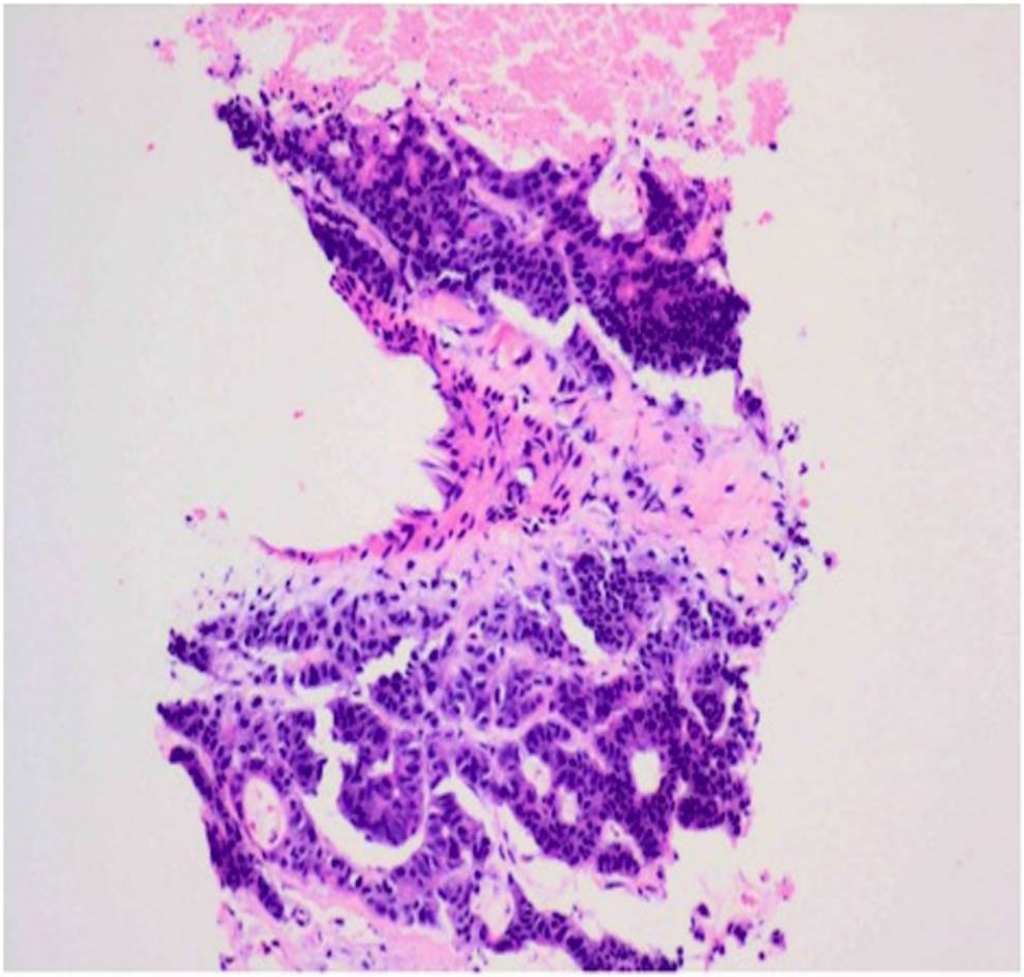

Figure 8: x100 The photomicrograph shows an intestinal type adenocarcinoma composed of acinarstructures set within a desmoplasticstroma with adjacent areas of coagulative necrosis.

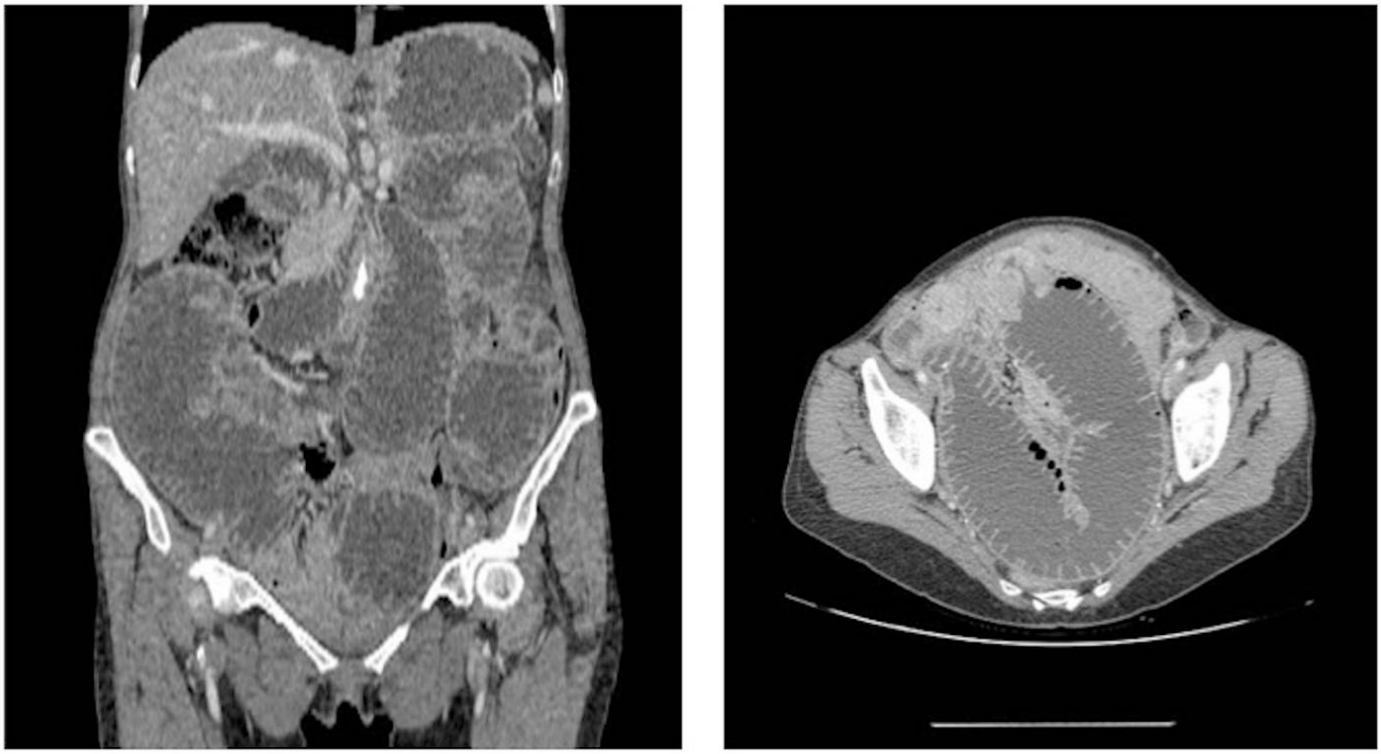

Figure 9: Small bowel obstruction secondary to adenocarcinoma of the small bowel. (a) Axial and (b) Coronal images demonstrate dilated small bowel loops caused by a small bowel neoplasm.

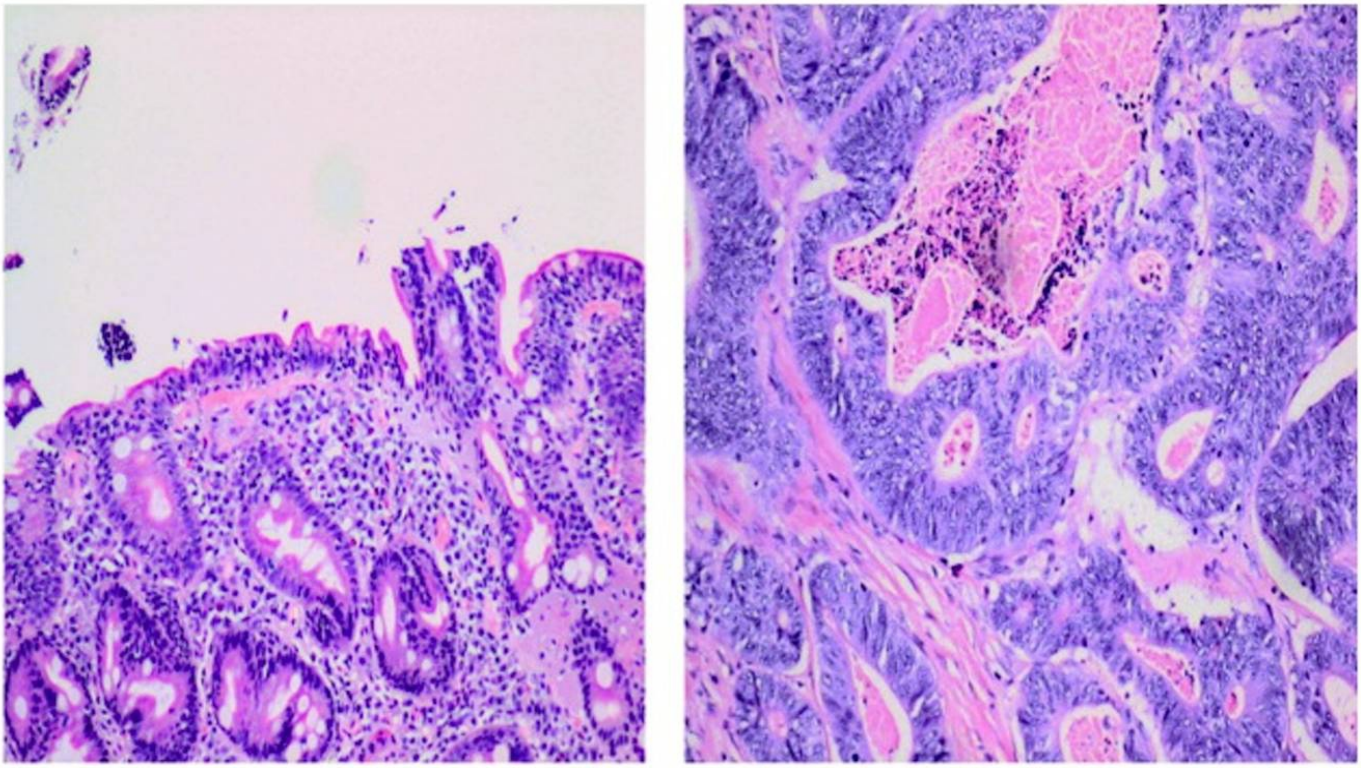

Figure 10: x100 The photomicrograph shows broad-based and stunted duodenal villi with an increased intraepithelial lymphocytic infiltrate amounting to more than 25 lymphocytes per 100 enterocytes. Also noted is an increased lymphoplasmacytic infiltrate in the lamina propria. (b) x100 The photomicrograph shows a malignant glandular neoplasm which consists of cribriform and acinar structures with central luminal “dirty” necrosis set in a desmoplasticstroma

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