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Case Report

Immunoglobulin G4-related disease coexisting with rectal cancer: a case report

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Abstract: So far, at least 12 cases of immunoglobulin G4 related disease (IgG4-RD) coexisting with colorectal cancer have been reported in the literature, but IgG4-RD with rectal cancer is still extremely rare. In addition, recently, the correlation between IgG4-RD and malignancy strongly motivates immunologists and pathologists to conduct further research. In this case study, we present a case of IgG4-RD with rectal cancer and review the pathological characteristics of IgG4-RD and discuss the association between IgG4-RD and malignancy. Indeed, the relationship between IgG4-RD and malignancy is controversial, but we remind physicians that they should be aware of the possible coexistence of malignancy among IgG4-RD patients.

Keywords: Immunoglobulin G4 related disease, rectal cancer, malignancy, pathology

Introduction

IgG4-RD is demonstrated as a class of chronic inflammatory disorders characterized by insidious onset and the impairment of multiple systemic organs, which appear more often in older males [1]. The organic lesions of IgG4-RD involve the pancreas, the lachrymal gland, the salivary glands, the hepatobiliary tract, the retroperitoneal tissues, the kidney, the lungs, the pituitary gland, and the thyroid, etc. [2] with the manifestation of enlargement and sclerosis. Laboratory and pathological examination, respectively, disclose a raised serum IgG4 level and the infiltration of numerous IgG4 positive plasmocytes, and storiform fibrosis at the site of the lesion [3]. Glucocorticoid is a first-line drug to treat IgG4-RD; however, the disease is more likely to recur as soon as glucocorticoid is reduced or withdrawn [4]. Inexperienced clinicians might initially misdiagnose the enlarged lesion caused by IgG4-RD as a tumor; however, with an increasing number of reports on IgG4-RD coexisting with a malignancy, the correlation of between these two diseases has sparked much interest among investigators, but they have no definite inclusions about the association between IgG4-RD and malignancy. There have been at least 12 cases describing IgG4-RD occurring with colorectal cancer reported in the literature. The case we describe of IgG4-RD with rectal cancer here complements the earlier reports, which show the need for more research on the association between IgG4-RD and malignancy.

Presentation of case

In this case, the client, a 74-year-old elderly male, had a complicated triphasic disease course.

First phase: detection of pathogeny: Five years ago, the client was admitted to the hospital for jaundice and abdominal distention. A physical examination indicated no obvious palpable masses in the abdomen. A qualitative exam of urine protein was 1+, the serum amylase level was 118 U/L (15-115); the serum glucose level was 8.98 mmol/L (3.89-6.11); the total bilirubin and direct bilirubin were elevated at 359.53 umol/L (5.1-17.1) and 342.62 ummol/L (1.7-6.8); the serum IgG level was elevated at 40.9 g/L (7.0-15.0); complement C3 was decreased

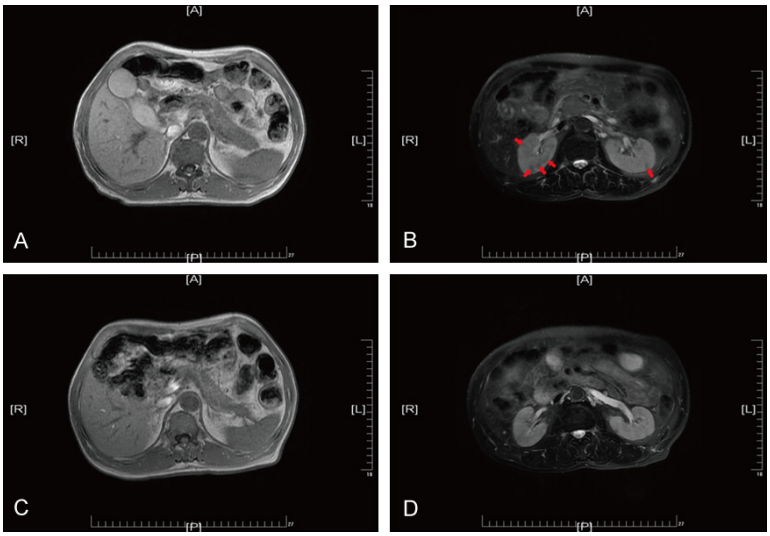

Figure 1. MRI of the abdomen (A and C were T1 MRI) (B and D were T2-fs MRI). (A) The pancreas was diffusedly thickened and enlarged, with a blunt appearance like sausage; the common bile duct, gallbladder, intrahepatic bile duct were all mild-to-moderate dilated. (B) The size and appearance of the bilateral kidneys were both normal, but a multiple patchy reduced signal intensity area was observed in the renal parenchyma (red arrows). (C) The pancreas was mildly enlarged, but the pancreatic duct, common bile duct, gallbladder, and intrahepatic bile duct showed no obvious dilatation. (D) The size and appearance of bilateral kidney both showed no apparently abnormal signs.

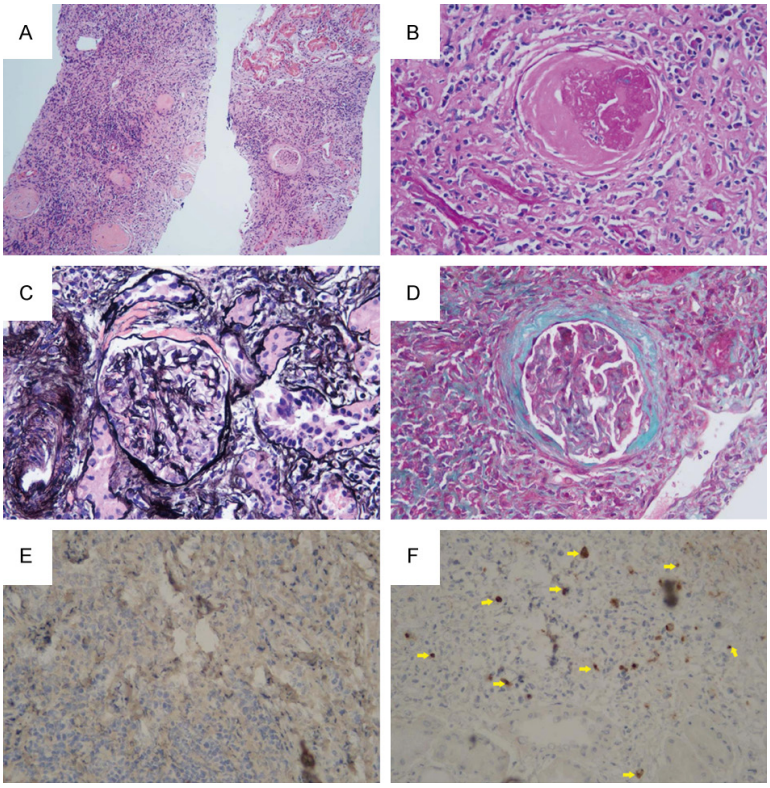

Figure 2. Histopathological findings of renal biopsy. A: HE staining (magnification ×100) a large body of interstitial lymphocyte infiltration; B: PAS staining (magnification ×200) glomeruli sclerosis; C: PASM staining (magnification ×200) capillary loops revealed opening; no obvious thickening of the basement membrane; D: Masson staining (magnification ×200) no visible fuchsinophilic protein deposition in glomeruli; E: Immunohistochemistry (magnification ×100) abundant IgG positive interstitial plasmacyte infiltration; F: Immunohistochemistry (magnification ×100) the brown-stained cells were IgG4 positive plasmacytes (yellow arrows); the ratio of IgG4 positive plasmocyte/IgG positive plasmocyte was >40% and the number of IgG4 positive plasmocyte was >10/high power field.

at 0.45 g/L (0.79-1.52); the C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were elevated at 22.40 mg/L (0-10) and 74 mm/h (0-15); the serum tumor maker CA-199 was increased at 147.9 U/ml (0-37.0); however, antinuclear antibody, anti-dsDNA, anti-ENA, and vasculitis associated antibody were normal. An endoscopic retrograde cholangiopancreatography showed that pancreatic head was occupied by an unknown mass, which misled the endoscopist to make a suspicious diagnosis of pancreatic cancer, but PET-CT images showed that autoimmune pancreatitis and inflammatory nephritis were more likely. Sequential laboratory studies found serum IgG4 levels elevated at 13.8 g/L(0.03-2.01) and an abdominal MRI was consistent with the typical images of IgG4-related pancreatitis and nephritis (**Figure 1A** and **1B**). Combining the result of serology and imaging, the patient was ultimately confirmed as having IgG4-RD (IgG4 related pancreatitis and nephritis). After of the administration of glucocorticoid and cyclophosphamide, the symptom of jaundice disappeared, and

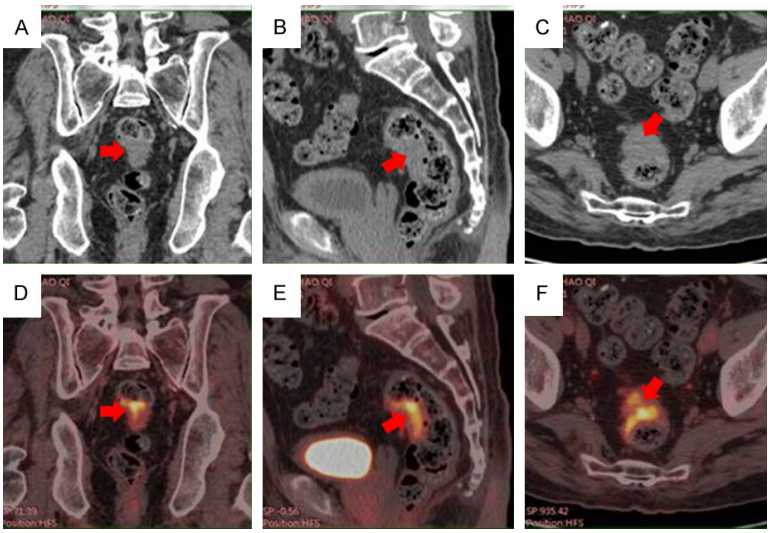

Figure 3. PET findings. (A and D), (B and E), (C and F) were coronal, sagittal, horizontal planes of abdomen in PET examination, respectively. In (D-F) the high-density radionuclide region indicated a probable rectal malignancy (red arrows).

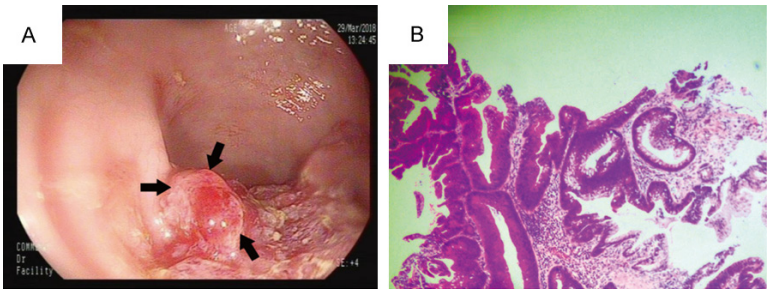

Figure 4. A: The colonoscope examination showed there was an irregularly-shaped mass in the anterior rectal wall, approximately 8 to 12 cm from the anal margin, which was fragile and easily bleeding after being touched (black arrows). B: HE staining (magnification ×100) had a pathological finding that indicated the histopathology of the rectal mass was consistent with the impression of intramucosal carcinoma.

MRI imaging showed an improvement of the pancreas and kidney (**Figure 1C** and **1D**). The patient constantly maintained glucocorticoid therapy after discharged from hospital.

Second phase: recurrence and aggravation: The client interrupted glucocorticoid therapy one year ago. Three months ago, he was admitted to hospital because his serum creatinine level was elevated, and laboratory tests showed his 24-hour urine protein rose at 2.34 g/24 h (0-0.12). His serum creatinine and urea nitrogen levels were high at 368.46 umol/L (44.00-133.00) and 13.25 mmol/L (2.80-7.10). His serum β2-microglobulin was 15894 ng/ml (604.0-2157.0); the serum Kappa and Lambda light chain were 10.93 g/L (1.38-3.75) and 5.06 g/L (0.93-2.42). The patterns and titer of ANA were nuclear homogenization and 1:1000, respectively. Urine Bence-Jones protein, glomerular basement membrane antibody, and serum protein electrophoresis were all negative. The serum tumor makers were normal, among which the serum carcinoembryonic antigen (CEA) level was 4.59 ng/ml (0-5). CRP and ESR were raised at 148.49 mg/L (0-10) and 110 mm/h (0-15). The serum IgG and IgG4 were elevated at 40.24 g/L (7.0-15.0) and 16.00 g/L (0.03-2.01), but complements C3 and C4 were decreased at 0.39 g/L (0.79-1.52) and 0.03 g/L (0.20-0.40). The patient agreed to have a percutaneous renal biopsy, and the pathological outcomes indicated IgG4-related tubulointerstitial nephritis (**Figure 2**). With retreatment of glucocorticoid and cyclophosphamide, his serum creatinine level decreased but he was still on super-baseline, and we determined he had stage IV chronic kidney disease.

Third phase: detection of rectal cancer: One month later, the repeat testing of serum IgG4 level of the client had decreased to 4.99 g/L (0.03-2.01), but his fecal occult-blood testing was unexpectedly positive and his serum CEA level had increased from 4.59 ng/ml to 36.11 ng/ml within two months (normal range: 0-5). Then the patient received a PET-CT examination with the unfavorable result of the probability of rectal cancer with peritoneal metastases (**Figure 3**), which was pathologically confirmed as intramucosal carcinoma (**Figure 4B**). The client was finally diagnosed with IgG4-RD and rectal cancer with peritoneal metastases. At present, he takes glucocorticoid 20 mg once daily

and receives regular chemotherapy (FOLFOX: fluorouracil, leucovorin, and oxaliplatin).

Discussion

The client in this case had these symptoms: (1) an MRI image suggested a diffused enlargement of the pancreas; (2) a serum IgG4 level >1.35 g/L; (3) the client had an abnormal urine and renal dysfunction presentation (his 24 hour urine protein was 2.34 g/24 h; his serum creatinine level was 368.46 μmol/L; his evaluated glomerular filtration rate was 18.54 ml/min); (4) the histopathological outcomes of his renal biopsy indicated clear evidence of numerous lymphocyte infiltration; moreover, immunohistochemistry demonstrated an IgG4 plasmocyte infiltration, with the ratio of IgG4 positive plasmocytes/IgG positive plasmocytes >40% and the number of IgG4 positive plasmocytes >10/high power field. Among the characteristics above, (1) and (2) were matched with international consensus diagnostic criteria for autoimmune pancreatitis (ICDC) [5] proposed in 2011, and (2) (3) (4) were consistent with the renal-specific diagnostic criteria [6] proposed by the Japanese IgG4 team in 2011.

A focal nodule or diffuse tumefaction could occur in the lesion when patients suffer from IgG4-RD, so inexperienced physicians might misdiagnose IgG4-RD as carcinoma. However, with the continually advanced study of IgG4-RD, an increasing number of reports on IgG4-RD coexisting with malignancy have also appeared, which has inspired researchers to explore the complicated connection between IgG4-RD and malignancy. Mahajan et al. [7] disclosed that IgG4-RD was an autoimmune disorder; Shiokawa et al. [8] and Asano et al. [9] both considered that IgG4-RD might be a preneoplastic condition; Eitan et al. [10] summarized the relationship of autoimmune diseases and malignancy, and they concluded that the impaired immune surveillance that resulted from autoimmune diseases could increase the risk of malignancy. Yamamoto et al. [11] concluded that IgG4-RD was connected with malignancy, and according to the results of a follow-up study of 105 patients who suffered IgG4-RD who had a higher standardized incidence ratio (SIR) of malignancy than the general population. Shiokawa et al. [8] also reported a similar result in 108 patients with AIP. Asano et al. [9], in an analysis of 158 IgG4-RD patients after 12 years of follow-up, not only found that active IgG4-RD was a risk factor of the development of malignancy, but they also indicated that the incidence of malignancy reached the peak within one year after the diagnosis of IgG4-RD. In recent years, several investigators [12, 13] evaluated the risk and the type of malignancy among IgG4-RD patients, whose findings also supported the conclusion that IgG4-RD patients had higher of probability of getting cancer. On the contrary, Hirano et al. [14] analyzed 113 IgG4-RD patients in the mean follow-up periods of 73 months and concluded that IgG4-RD is not correlated with the formation of malignancy at all, and their team found no significant differences between the SIR of malignancy among IgG4-RD patients and the general population, since they initially excluded the subjects who were concurrently diagnosed as IgG4-RD complicated with malignancy and initially excluded the subjects who were diagnosed as malignancy concomitantly with IgG4-RD to avoid selection bias.

Considering the information above, the development of malignancy associated with IgG4-RD remains controversial. Standing on the statistical aspect of screening subjects, the conclusion of Harano et al. [14] is more rigorous than those of other investigators, but the time window regarding how long IgG4-RD can cause malignancy has no accurate definition, so that we cannot ignore the conclusions of Asano et al. [9] As for the elderly patient described in this case study, his old age would have been the risk factor for the malignancy, plus his long interval (approximately 5 years) of occurrences of IgG4-RD and rectal cancer, about which no similar cases have been reported, leads us to assume the development of rectal cancer in this client is independent of IgG4-RD. However, we could not rule out the probability that the relapse of IgG4-RD in this patient caused the malignancy, so all of our conjectures need further study. Though the correlation between IgG4-RD and malignancy is controversial, physicians ought to be cautious of its development among IgG4 patients. It is beneficial for detecting malignancy promptly and prolonging the survival of IgG4-RD patients with the assistance of all available examination approaches.

Conclusion

In this case study, we report the process of a patient with IgG4-RD with rectal cancer, by reviewing the diagnostic criteria of IgG4-related

pancreatitis and IgG4-related tubulointerstitial nephritis and then discussing the association between IgG4-RD and malignancy. As for the client, he was definitely diagnosed as having IgG4-RD (IgG4 related pancreatitis; IgG4 related tubulointerstitial nephritis) and rectal cancer, and we all consider that both of the diseases are independent of each other; however, we remind clinical physicians that they should be cautious of the coexistence of malignancy among the IgG4-RD patients.

Disclosure of conflict of interest

None.

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