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CASES WITH A MESSAGE

Elevated CA-125 in IgG4 mesenteritis: a red herring or a disease biomarker? Case report and literature review

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Abstract

Mesenteric panniculitis (MP) is a rare chronic disease characterized by inflammation and subsequently fibrosis of adipose tissue of the omentum. Only recently it has been associated with IgG4-related disease. Cancer antigen 125 (CA-125) is a high-molecular mass glycoprotein, traditionally associated with ovarian cancer, although it can be elevated in other conditions. Herein we describe a case of a 56-year-old man with IgG4 related mesenteric panniculitis associated with very high levels of CA-125 at the onset of disease. The CA-125 levels corresponded to clinical disease activity and improved with steroid therapy and rituximab. A literature review was performed concerning possible association of MP, IgG4-related disease and CA-125. The review of literature suggests that high levels of CA-125 can be raised in non-malignant, inflammatory conditions including IgG4-related mesenteritis and can improve with treatment.

Keywords Panniculitis, peritoneal · CA-125 antigen · Mesentery · Peritoneum · Inflammation · Immunoglobulin G · Biomarkers, tumor

Introduction

Cancer antigen 125 (CA-125), a large transmembrane glycoprotein derived from ovarian epithelial cells and mesothelial linings, is a widely accepted biomarker for ovarian cancer. In this respect, it has become an important component of the diagnostic pathway for ovarian cancer, despite its relatively poor specificity and sensitivity [1]. Lack of awareness about the role and limitations of CA-125 can lead to clinical uncertainty, increased patient anxiety and costly additional testing. Reports of less common causes of CA-125 elevation therefore add to the existing evidence-base and are helpful in critically evaluating its clinical meaning. Herein we report a case diagnosed with IgG4-related mesenteric panniculitis (MP) in which very high levels of CA-125 were found. MP is a rare condition characterized by chronic, fibrotic inflammation of the bowel mesentery. Some cases of MP are in fact thought to represent rare manifestations of IgG4-related disease (IgG4-RD) [2]. IgG4-RD is another chronic inflammatory disease whereby IgG4-positive plasma cells and lymphocytes infiltrate tissues. It has been described in virtually every organ system and can affect one or multiple organs at the same time. Manifestations include auto-immune pancreatitis and disease affecting the respiratory system, salivary glands, and kidneys, among others [3].

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In light of this, a systematic literature review was performed to investigate for associations between CA-125, MP and/or IgG4-RD, to obtain insights into possible common pathophysiological mechanisms and potential clinical implications.

Clinical case

The patient, a 56-year-old man, was initially admitted to hospital with a 2–3 week history of abdominal pain, vomiting, and constipation. As part of the diagnostic work-up inflammatory markers were raised (ESR 64 mm/h, CRP 64 mg/mL) and a generic panel of tumor markers revealed a CA-125 of 1358 IU/mL (normal < 35). CT abdomen showed omental thickening and spotty peritoneal hyperintensities involving the entire anterior lower abdominal wall, measuring approximately 3.2 cm in maximum thickness. There was evidence of moderate ascetic fluid, with swelling of the mesentery and enlarged lymph nodes, indicating MP (Fig. 1a). Histology of the omentum following an emergency laparotomy was compatible with IgG4-RD (Fig. 1b). The immunologic tests (ANA, ENA, rheumatoid factor, anti-CCP) were negative while the serum IgG4 was high (416 mg/dL, range 3–201). Based on the clinical, radiological and histopathological findings, a diagnosis of IgG4-related MP was made and steroids (0.5 mg/kg) were started. There was excellent clinical, radiological (i.e. reduction in thickness of the omentum) and biochemical response (CRP 10 mg/ml, IgG4 228 mg/dL) within 2 months of treatment-onset, also in CA-125 levels (100 IU/mL). Unfortunately, following 3 months of disease remission, there was a relapse of clinical symptoms prompting treatment with Azathioprine (2.5 mg/kg) and eventually Rituximab (1000 mg × 2 every 6 months) as steroid sparing-agents. During this relapse, the CA-125 level again rose to 300 IU/mL. Currently the patient remains clinically and biochemically in remission on Prednisone 5 mg/day and Rituximab.

Methods

The databases searched were MEDLINE, EMBASE, Web of Science, and Scopus, looking for all literature published up to 8 January 2018. A comprehensive search strategy with terms linked to the above topics was developed by two of the authors and a librarian.

Mesenteric panniculitis

Search terms "((mesentery or mesenteric or sclerosing or liposclerotic or retractile or peritoneum or peritoneal or mesocolic) AND (mesenteritis or panniculitis or lipodystrophy or lipomatosis or lipogranuloma*))" were used, to catch all descriptions of idiopathic mesenteric inflammation, including MP and sclerosing mesenteritis (SM).

In MEDLINE, these terms were combined with "OR MeSH terms "Mesentery", "Peritoneum", and "Panniculitis, peritoneal". The same search was executed in EMBASE (using MeSH terms "Mesentery", "Peritoneum", "Panniculitis" and "Lipodystrophy"), SCOPUS (no MeSH terms), and Web of Science (no MeSH terms).

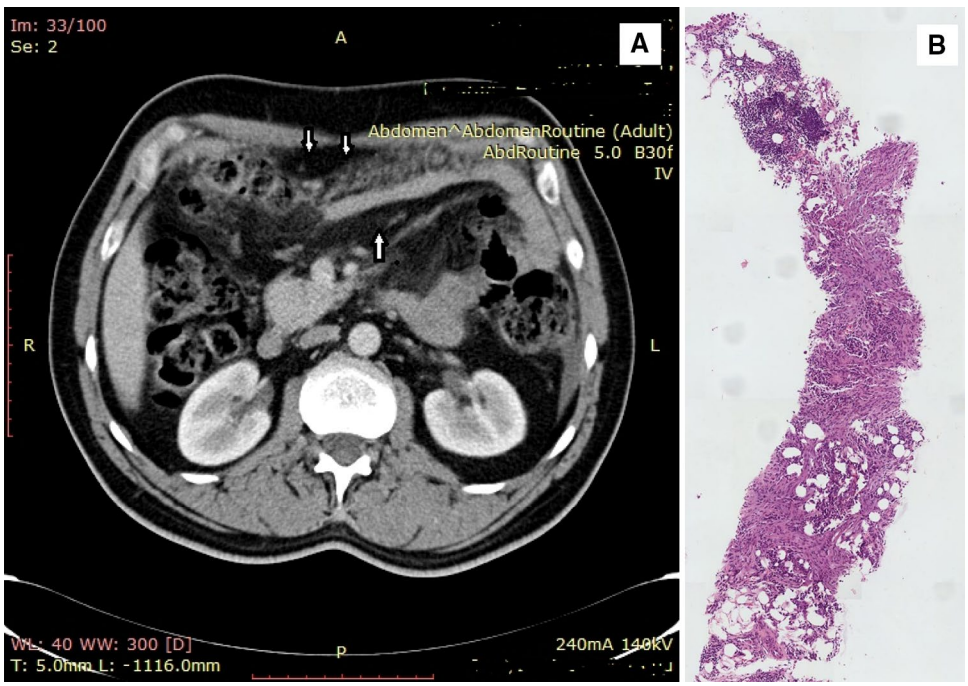

Fig. 1 **a** Abdominal CT showing nodular thickening of the greater omentum with strands of ill-defined soft tissue due to omental inflammation (arrows). **b** Histology results: biopsy of omentum with haematoxylin and eosin stain showing dense infiltration of lymphocytes, eosinophils and IgG4 positive plasma cells, scattered histiocytes and dendritic cells. Hyaline basement membrane material deposited between cells. "Storiform fibrosis" observed

Table 1 Clinical and laboratory characteristics of cases of IgG4-RD and MP

References	Patient demographics	Main diagnosis	Serum CA-125 (U/mL)	Serum IgG4	Other tumour markers	Presence of effusions
Tong et al. [4]	43 F	IgG4-RD	↑ (1065)	↔ (1.25 g/L)	CA 19-9 ↑, AFP ↑, CEA ↔	Ascites, pleural and pericardial effusions
Khosla et al. [5]	72 M	AIP	↑ (196.4)	↑ (144 mg/dL)	CA 19-9 ↔, CEA ↔	N/A
Thomas et al. [6]	46 F	AIH, AI myositis	↑ (417)	43 (units not specified)	CA 19-9 ↑	Ascites
Zhou et al. [7]	24 F	IgG4-RD (lung)	↔	↑	CA 19-9 ↔, CEA ↔, CA-153 ↔	Pleural effusion
Fengqing et al. [8]	Cohort study of 22 patients	IgG4-RD	↑ in 12/22	↑ in 22/22 (mean 6.5 g/L; range 2.1–16.4 g/L)	CA 19-9 ↑ in 6/22	N/A
Cheng et al. [9]	45 M	AIP	↑ (77.5)	↑ (3000 mg/dL)	CA 19-9 ↔	Ascites, pleural effusions
Liu et al. [10]	41 M	IgG4-RD (lung)	↔	↑ (307 mg/dL)	CA 19-9 ↔, CEA ↔, PSA ↔, NSE ↔	No
Graham and Harvin [11]	66 F	IgG4-RD (SM)	↔	↑ (103 mg/dL)	CA 19-9 ↔, CEA ↔	Ascites
Ghadir et al. [12]	70 M	AIP	↔	↑ (187 ng/mL)	CA 19-9 ↔, CEA ↔	N/A
Dogaru et al. [13]	60 F	SM	↑ (295.5)	N/A	CA 19-9 ↔, AFP ↔, CEA ↔	N/A
Buyukbarak et al. [14]	38 F	SM	↑ (44.5)	N/A	CA 19-9 ↔, AFP ↔, CEA ↔, CA 153 ↔	Ascites
Malter et al. [15]	57 F	MP	↑ (630)	N/A	N/A	Ascites
Xiaoting et al. [16]	Retrospective study of 7 patients (3 F, 4 M)	IgG4-RD (lung)	↑ in 3/3 F (46.54, 156, 85.58)	↑ in 3/3 F (271, 600, 352 mg/dL)	CA 19-9 and CEA ↑ in 1/3 F	No
			↔ in 4/4 M	↑ in 4/4 M (256, 389, 1410, 168 mg/dL)	CEA ↑ in 1/4 M	Pleural effusion in 1/4 M
Current report	56 M	IgG4-related MP	↑ (1358)	↑ (416 mg/dL)	CA 19-9 ↔, AFP ↔, CEA ↔	Ascites

AI autoimmune, *AIH* autoimmune hepatitis, *AIP* autoimmune pancreatitis, *SM* sclerosing mesenteritis, *N/A* details not available

IGG4-RD

Search terms for IGG4-RD were "Immunoglobulin G4 or igg4 or igg-4 or ig-g4 or gamma G4" in all databases, combined with "OR the MeSH term "Immunoglobulin G4" in EMBASE only.

These results were then filtered for papers mentioning CA-125 by combining these searches with "AND (CA 125 or ca125 or antigen 125 or CA12-5 or CA-12-5 or antigen 12-5 or MUC16 or MUC 16 or mucin 16)" in all databases, as well as with "OR the MeSH term "CA-125 Antigen" in MEDLINE and EMBASE.

This search revealed papers in which the above terms were either mentioned in the abstract or listed as subject headings.

Literature screening was performed by two independent reviewers. Inclusion criteria: a final diagnosis of either MP or IGG4-RD (including AIP and other organ-specific manifestations) and a recorded CA-125 level. Reports on raised CA-125 in the context of malignancy were excluded.

Results

We identified 13 relevant citations describing a total of 40 cases of IgG4-RD (including autoimmune pancreatitis, autoimmune hepatitis, and IgG4-related lung disease) or MP, in which the CA-125 level was also reported (Table 1).

Reports included in the table are of not only MP but also SM. Recent reports suggest that MP relates to more stable and characteristic radiologic changes whereas SM has more

atypical radiology and a more aggressive clinical course [17]. Both conditions fall within the spectrum of idiopathic mesenteric inflammation.

Discussion

CA-125 was raised in 22/40 patients: 3/4 cases with known MP, and 19/36 with known IgG4-RD. While this is the first review looking at these specific conditions, there have been reports of raised CA125 in numerous other benign non-gynaecological conditions, including tuberculosis, peritonitis, pancreatitis, and nephrotic syndrome [18]. Inflammation, mechanical stress and presence of serosal effusions have been suggested as potential reasons for the raised CA-125 [19]. A variety of cells produce and secrete CA-125, including mesothelial (pleural, pericardial, peritoneal, endometrial) and non-mesothelial (amniotic membrane, tracheobronchial and cervical epithelium) cells. It is therefore not surprising to see a correlation between multiple types of serosal fluid (peritoneal, pleural, or pericardial) and high CA-125 levels [20]. A potential explanation for this could be that mechanical stress on mesothelial cells, by external pressure (eg from fluid) or direct damage (eg surgical intervention), increases CA-125 production and secretion, with inflammation being an additional cause [19]. Our case supports the existing literature of an association between CA-125 and serosal effusions. However, literature also reports on the presence of effusions in the context of a normal level of CA125, as well as cases in which CA-125 is raised without evidence of serosal involvement (Table 1). What seems to be a common factor in these cases is inflammation, with likely consequent irritation of CA-125 expressing mesothelial tissues. It is possible that when these cells are damaged, either mechanically or by inflammatory processes, CA-125 production and/or secretion increases, raising the serum level, and can be accompanied by the accumulation of serosal fluid which provides another pathway for it to enter the bloodstream. The implications of these observations are twofold. CA-125 is frequently tested in patients who present with non-specific symptoms potentially suggestive of malignancy. Particularly in female patients, elevated levels raise suspicion for ovarian cancer, resulting in invasive further investigations. Our literature review identified two cases in which female patients underwent laparotomies under the presumptive diagnosis of ovarian carcinoma only to reveal MP [14, 15]. Given the wide differential diagnosis in this type of cases, even in light of raised CA-125 levels, performing minimally invasive investigations such as imaging and laparoscopic biopsy, could help rule-out less sinister causes. Generally, the sensitivity, specificity, and positive predictive value of raised CA-125 levels are relatively low, and we call for cautious interpretation with expert guidance [1]. In the case of inflammatory conditions such as the ones described in this report, there is perhaps an additional role for CA-125 as a potential biomarker of active disease. Aside from our own case report, only one other mentioned a reducing post-treatment CA-125 level [4]. We conclude that there might be a role for CA-125 as a marker of active disease and response to treatment. Further evidence is needed to draw firm conclusions on the consistency of this phenomenon.

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Author contributions SP and GN were directly involved in the care of the patient. SP and EN conceived the idea to write the specific case as a case report and literature review. MMM and IP designed and executed the literature search, and drafted the first version of the manuscript with guidance from EN and SP. All authors discussed the results and commented on the manuscript.

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Compliance with ethical standards

Conflict of interest The authors have declared no conflicts of interest.

Informed consent The patient consented to publication of his case.

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