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Persistent Unexplained CA125 and CA19-9 Elevation During Gynecological Follow-Up: A Diagnostic Challenge Beyond Tumor Marker Non-Specificity

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Patient: Female, 68-year-old
Final Diagnosis: MPO
Symptoms: None
Clinical Procedure: —
Specialty: Obstetrics and Gynecology
Objective: Rare coexistence of disease or pathology

Background: Tumor marker elevation during surveillance after borderline ovarian tumor surgery commonly raises concern for recurrence. However, CA125 and CA19-9 are nonspecific and may also increase in extrapelvic inflammatory disease.

Case Report: A 66-year-old woman underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy, omentectomy, and partial rectal resection for bilateral serous borderline ovarian tumor, International Federation of Gynecology and Obstetrics stage IB. Tumor marker levels remained normal for several years after surgery. Eight years later, CA125 increased to 65 U/mL and CA19-9 to 140.5 U/mL, with CA19-9 subsequently peaking at 610 U/mL. Repeated pelvic magnetic resonance imaging, PET-CT, cytologic assessment of the vaginal cuff, upper gastrointestinal endoscopy, and hepatobiliary and pancreatic evaluation showed no evidence of recurrent borderline ovarian tumor or other malignancy. During the same period, interstitial lung disease progressed radiologically, respiratory symptoms worsened, and serologic testing demonstrated myeloperoxidase-antineutrophil cytoplasmic antibody positivity. Progressive myeloperoxidase-antineutrophil cytoplasmic antibody-associated interstitial lung disease was considered a plausible extrapelvic explanation for the persistent marker elevation. Pirfenidone and low-dose prednisolone were initiated, and although tumor marker levels initially continued to rise, they subsequently decreased from their peak values during follow-up while repeated gynecologic evaluation remained negative.

Conclusions: This case highlights a potential limitation in the interpretation of tumor marker elevation during borderline ovarian tumor surveillance. Persistent CA125 and CA19-9 elevation does not necessarily indicate gynecologic recurrence when repeated pelvic evaluation is negative. In selected patients, pulmonary or systemic inflammatory disease may be considered according to symptoms, imaging findings, and overall clinical context.

Keywords: Lung Diseases • Ovary • Gynecology • Vasculitis
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Introduction

Tumor marker surveillance is a standard component of follow-up in patients treated for borderline ovarian tumors (BOTs), particularly given the risk of late recurrence. Postoperatively, CA125 and CA19-9 are routinely monitored, and elevations in these markers typically prompt additional imaging studies or clinical reassessment. Even though the nonspecific nature of these tumor markers is well recognized, interpretation can be challenging when imaging does not support recurrence. BOT is reported to recur in approximately 5% to 10% of cases, with most recurrences occurring within 5 to 10 years after initial treatment [1].

Several non-gynecologic and benign conditions, including interstitial lung disease (ILD), have been reported to cause elevations in CA125 and CA19-9 [2,3]. Tumor marker elevation has also been reported in patients with myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA)-associated ILD [4]. Such diagnostic overlap may complicate differentiation from tumor recurrence during gynecologic surveillance.

We report a case of a patient with a history of bilateral serous BOT who presented with elevated CA125 and CA19-9 levels 8 years after surgery. Despite extensive imaging, no evidence of recurrence was found, and progressive MPO-ANCA-associated ILD was considered a plausible extrapelvic explanation for the persistent marker elevation. To our knowledge, reports describing ANCA-associated ILD identified through tumor marker elevation during BOT surveillance remain extremely limited. This case highlights the clinical challenge of interpreting tumor marker elevation in long-term BOT follow-up and underscores the importance of considering non-malignant, extrapelvic conditions in the differential diagnosis.

Case Report

A 66-year-old woman presented to the gynecology department with complaints of progressive abdominal distension over the preceding 3 months. Magnetic resonance imaging (MRI) revealed a large right ovarian cystic mass measuring approximately 30 cm in diameter, with no evident solid components (**Figure 1A**). A multi-cystic lesion with some solid portions was also identified in the left ovary. No apparent pelvic lymph node enlargement or distant metastases were detected. Measurement of initial serum tumor markers showed elevated levels of CA125 at 732.4 U/mL, CA19-9 at 13.1 U/mL, and carcino-embryonic antigen at 2.2 ng/mL.

Surgical Treatment and Histopathology

Twelve days later, the patient underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy, omentectomy, and partial rectal resection followed by intestinal anastomosis, due to suspected tumor invasion into the rectal wall. The intraoperative blood loss was estimated at 677 mL. The right ovarian tumor weighed 4700 grams. Histopathological examination of the surgical specimens revealed bilateral serous borderline tumors with a background of adenofibroma (**Figure 1B**). No malignant epithelial components were identified, and the tumor exhibited mild nuclear stratification and loss of polarity. Cytologic examination of ascitic fluid was negative. The uterus was unremarkable, and no tumor invasion was observed on the serosal surface of the rectum. Omental tissue was free of tumor involvement. Based on these findings, the disease was staged as International Federation of Gynecology and Obstetrics (FIGO) Stage IB (1988 classification).

Follow-Up and Clinical Course

Five years later, the patient was referred to respiratory medicine after a computed tomography (CT) scan indicated interstitial pneumonia. Between the initial surgery and 7 years later, the patient's tumor marker levels, including CA125 and CA19-9, remained within the normal range. However, the next year, 8 years after the initial surgery, laboratory results revealed elevated levels of CA125 at 65 U/mL and CA19-9 at 140.5 U/mL. The serial changes in tumor markers are shown in **Figure 2**. CA19-9 subsequently increased further, peaking at 610 U/mL.

Contrast-enhanced CT scans showed no evidence of neoplastic lesions in the pancreas or gallbladder. There was no ascites, and no findings suggestive of malignancy. Upper gastrointestinal endoscopy also revealed no abnormalities. As part of gynecologic surveillance, including positron emission tomography (PET)-CT and cytologic examination of the vaginal cuff, no evidence of tumor recurrence was detected. Chest CT also demonstrated progression of fibrotic ILD (**Figure 1C**).

However, 9 years after the initial surgery, progressive respiratory symptoms, worsening fibrotic ILD on the chest CT and serological MPO-ANCA positivity led to the clinical diagnosis of MPO-ANCA-associated ILD. No lung biopsy was performed; therefore, the diagnosis was based on clinical, radiological, and serological findings without histopathological confirmation. Treatment was initiated with pirfenidone (1200 mg/day) and low-dose prednisolone (5 mg/day). Despite ongoing therapy, the patient's tumor markers continued to rise gradually. A year later (10 years after the initial surgery), repeat PET-CT showed no definitive evidence of malignancy. Radiologic findings demonstrated chronic progression of ILD (**Figure 1D**).

During follow-up, both CA125 and CA19-9 gradually decreased from their peak values, although they remained above the normal range. Repeated evaluation continued to show no evidence of recurrent disease (**Figure 2**).

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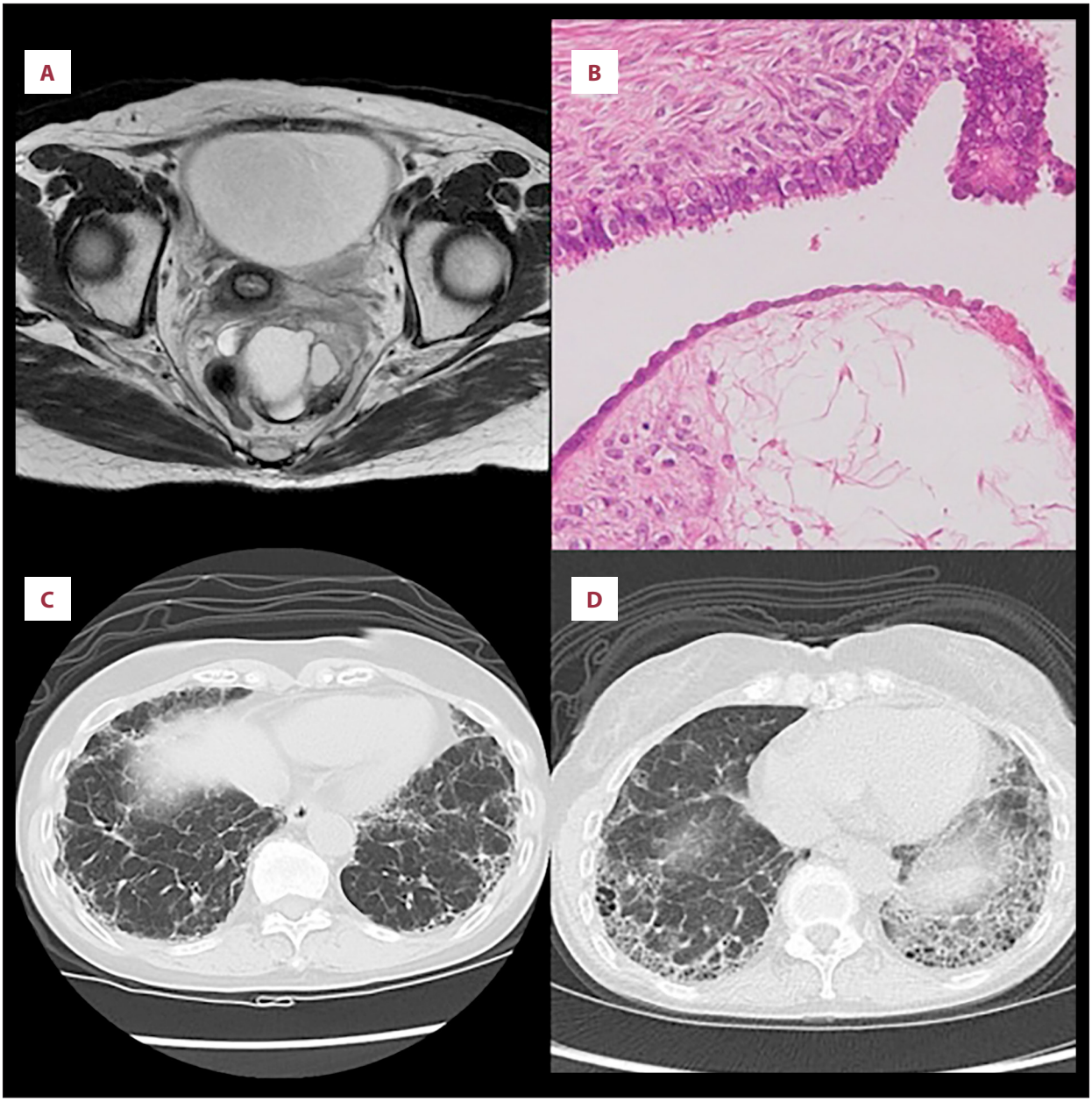


Figure 1. Pelvic imaging and histopathology of serous borderline ovarian tumor and MPO-ANCA-associated ILD. (**A**) Pelvic MRI at the initial presentation demonstrating a large multilocular cystic ovarian mass (approximately 30 cm in maximum diameter), which was surgically resected and diagnosed as serous borderline ovarian tumor. (**B**) Histological section of the initial serous borderline tumor resected from the ovary, demonstrating hierarchical papillae with stratified epithelium and mild nuclear atypia (H&E stain, × 100). (**C**) High-resolution CT scan of the chest (lung window) revealing diffuse ground-glass opacities and reticular shadows consistent with ILD. (**D**) Follow-up CT scan showing progression of bilateral basal fibrotic changes. MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibody; ILD, interstitial lung disease; MRI, magnetic resonance imaging; H&E, hematoxylin and eosin; CT, computed tomography.

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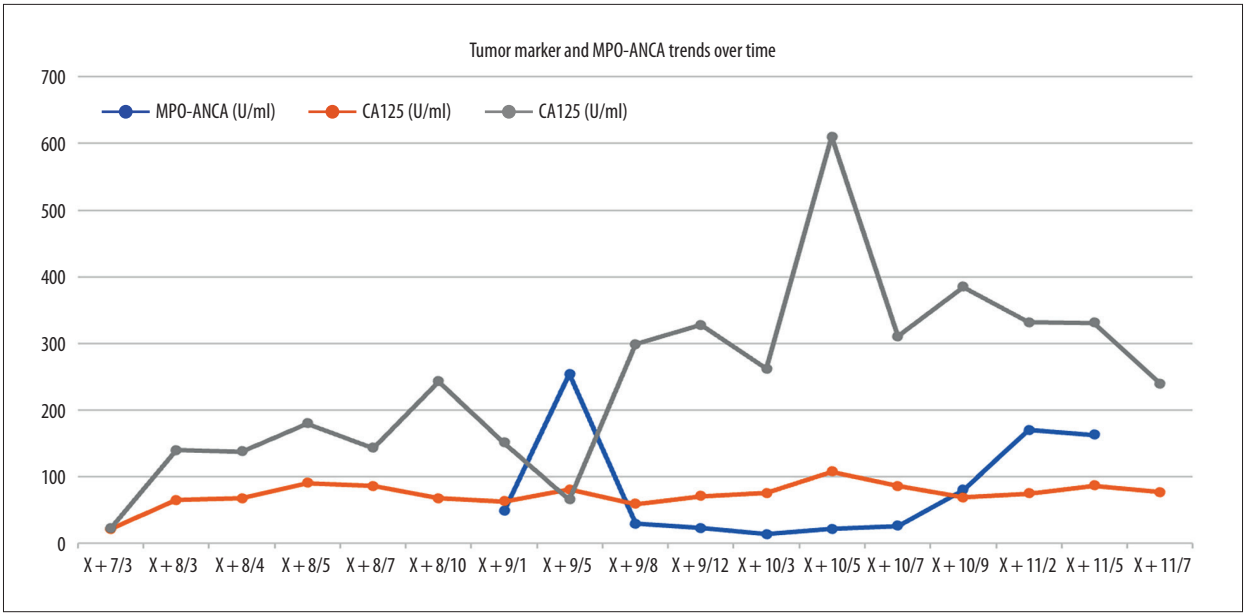


Figure 2. Tumor marker and MPO-ANCA trends over time. Longitudinal trends of serum tumor markers (CA125 and CA19-9) and MPO-ANCA following surgery for borderline ovarian tumor. Year X denotes the year in which the patient first visited our institution. Subsequent years are denoted as X+n. The upper reference limits provided by the testing laboratory were ≤35 U/mL for CA125, ≤37 U/mL for CA19-9, and < 3.5 U/mL for MPO-ANCA. MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibody.

Discussion

In long-term BOT surveillance, persistent CA125/CA19-9 elevation with negative pelvic imaging should prompt consideration of extrapelvic causes, including inflammatory and autoimmune conditions such as MPO-ANCA-associated interstitial lung disease.

For gynecologists, CA125 and CA19-9 are valuable markers for detecting recurrence of ovarian cancer, and their well-recognized nonspecific nature is routinely considered in clinical practice. Nevertheless, recurrence is often first suspected because of an elevation in CA125 levels before physical examination findings become apparent [1].

BOTs generally have a favorable prognosis, with a 5-year survival rate of approximately 95% for serous types and nearly 100% for mucinous types [5]. Although tumor markers such as CA125 are frequently monitored in BOT follow-up, their precise role remains debated. Recurrence rates of BOT have been reported at approximately 5% to 10%, with some studies noting recurrence even beyond 10 years post-treatment, particularly with mucinous subtypes [6].

CA125 is primarily produced by mesothelial cells lining the pleura, peritoneum, and pericardium, and its expression increases in response to serosal inflammation. While elevated in ovarian and endometrial malignancies, CA125 can also rise in various non-malignant conditions, including endometriosis, interstitial pneumonia, liver cirrhosis, and menstruation [2]. Similarly, CA19-9, which is secreted by pancreatic and biliary epithelium and expressed in respiratory epithelium, may be elevated in pancreatic cancer, mucinous ovarian tumors, and certain inflammatory or pulmonary diseases [7]. **Table 1** [2-4,8-16] summarizes selected malignant and non-malignant conditions associated with elevated CA125 and/or CA19-9.

In epithelial ovarian cancer, treatment decisions based solely on tumor marker elevation have not demonstrated a survival benefit, and current guidelines do not recommend initiating treatment solely on the basis of marker elevation [17]. Although BOT differs biologically and clinically from epithelial ovarian cancer, this principle reinforces the need for cautious interpretation of tumor markers. In BOT follow-up, CA125 and CA19-9 should be interpreted as adjunctive findings rather than definitive evidence of recurrence [6].

Several reports have described the ranges of CA125 and CA19-9 levels in ILD, ovarian cancer, and BOT, and notable overlap exists between inflammatory pulmonary disease and borderline tumors. Elevated CA125 and CA19-9 levels have been reported in patients with various forms of ILD, including MPO-ANCA-associated disease [3,4]. In patients with MPO-ANCA-associated vasculitis, Yang et al reported higher serum CA125 and CA19-9 levels in those with ILD than in those without ILD [4]. These findings suggest that elevation of these tumor markers may

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Table 1. Conditions associated with elevated CA125 and/or CA19-9 (selected examples).

Disease / condition (category)	CA125	CA19-9	Proposed mechanism (brief)	Key clinical clues / how to differentiate
MPO-ANCA-associated vasculitis with ILD (non-malignant)	↑	↑	Pulmonary/pleural inflammation; systemic inflammation	HRCT-ILD, MPO-ANCA+, inflammatory markers; no pelvic mass on imaging
ILD (non-malignant)	↑	↑	Airway/alveolar epithelial injury; inflammatory upregulation of glycoproteins	HRCT pattern; pulmonary symptoms; trend with inflammation/fibrosis
Peritoneum / pleura tuberculosis (non-malignant)	↑	(—)	Serosal inflammation (peritoneum/ pleura)	Ascites/effusion, lymphocyte-predominant fluid, ADA/IGRA, imaging
Liver cirrhosis with ascites (non-malignant)	↑↑	(↑)	Peritoneal stretch/irritation from ascites; reduced clearance	Ascites, portal HTN, LFT abnormalities; no focal malignancy on imaging
Cholangitis / benign biliary obstruction (non-malignant)	(↑)	↑↑	Cholestasis + biliary inflammation	Jaundice, biliary dilation, cholangitis signs; improves with drainage / antibiotics
Acute pancreatitis (non-malignant)	(↑)	↑	Pancreatobiliary inflammation	Epigastric pain, amylase / lipase, CT / MRI findings
Pelvic inflammatory disease / tubo-ovarian abscess (non-malignant)	↑	(↑)	Peritoneal inflammation	Pelvic pain/fever, WBC / CRP, imaging, response to antibiotics
Endometriosis (non-malignant)	↑	(↑)	Peritoneal irritation / inflammation; higher with extensive disease / adhesions	Cyclic pain, MRI/US findings; benign ovarian endometrioma
Ovarian epithelial cancer (malignancy)	↑↑	(↑)	Tumor burden ascites / peritoneal involvement	Adnexal mass, ascites; imaging + pathology
Endometrial cancer (malignancy)	↑	(↑)	Often reflects extrauterine spread / tumor burden (advanced disease)	Abnormal uterine bleeding, thickened endometrium; biopsy
Pancreatic cancer (malignancy)	(↑)	↑↑	Tumor-derived CA19-9; can be confounded by cholestasis	Pancreatic mass, biliary dilation, jaundice, weight loss

Symbols indicate qualitative tendencies rather than strict quantitative cutoffs: ↑, tends to be elevated; ↑↑, may be markedly elevated; (↑), occasionally elevated; and —, no consistent association. References supporting Table 1: ovarian epithelial cancer and CA125 [2]; ILD [3]; MPO-ANCA-associated vasculitis with ILD [4]; Liver cirrhosis/ascites and CA125 [8]; benign biliary obstruction/cholangitis and CA19-9 [9]; acute pancreatitis and CA19-9 [10]; pelvic inflammatory disease and CA125 [11]; endometriosis and CA125 [12]; pancreatic cancer and CA19-9 [13]; preoperative CA125 and extrauterine disease in endometrial cancer [14]; pulmonary or pleural tuberculosis and CA125 [15,16]. ADA, adenosine deaminase; IGRA, interferon-gamma release assay; HTN, hypertension; HRCT, high-resolution computed tomography; LFT, liver function tests; CT, computed tomography; MRI, magnetic resonance imaging; WBC, white blood cell count; CRP, C-reactive protein; US, ultrasonography; CA125, cancer antigen 125; CA19-9, carbohydrate antigen 19-9; ILD, interstitial lung disease; MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibody.

be associated with the underlying ILD rather than being specific for MPO-ANCA positivity.

In the present case, tumor marker elevation during BOT follow-up initially raised concern for recurrence or malignant transformation. However, the patient underwent careful longitudinal monitoring, including PET-CT, MRI, cytologic assessment of the vaginal cuff, and hepatobiliary and pancreatic evaluation. These examinations did not show evidence of recurrence or another malignancy. Progressive MPO-ANCA-associated ILD was therefore considered a plausible extrapelvic explanation for the persistent marker elevation. During follow-up after treatment for MPO-ANCA-associated ILD, both CA125 and CA19-9 decreased from their peak values. Although this temporal association may support MPO-ANCA-associated ILD as a possible contributor to the tumor marker elevation, it does not establish a direct causal relationship. In addition, MPO-ANCA titers do not necessarily correlate with ILD disease activity or

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fibrotic progression. Therefore, tumor marker levels should be interpreted together with respiratory symptoms and imaging findings rather than MPO-ANCA titers alone.

To our knowledge, reports describing MPO-ANCA-associated interstitial lung disease (ILD) emerging as an explanation for persistent CA125/CA19-9 elevation during long-term BOT surveillance are scarce in the gynecologic literature. Because ANCA-associated ILD may be associated with an unfavorable prognosis, particularly in patients with a usual interstitial pneumonia pattern, timely recognition is clinically important in appropriate contexts [18].

Although the non-specificity of CA125/CA19-9 is well recognized in gynecologic practice, the optimal next-step evaluation when pelvic imaging remains negative is not always clearly defined. While it is well known that tumor markers such as CA19-9 and CA125 are nonspecific, their differential diagnosis is sometimes not given careful consideration. This tendency may be particularly pronounced in fields outside one's area of expertise.

This case illustrates an interface between 2 clinical perspectives that are considered separately: the gynecologic interpretation of tumor marker elevation during BOT surveillance and the pulmonary literature describing tumor marker elevation in MPO-ANCA-associated ILD.

For gynecologists, the educational value of this case lies in recognizing that persistent CA125 and/or CA19-9 elevation may represent a diagnostic blind spot when repeated pelvic evaluation is negative. In such selected situations, awareness of pulmonary and systemic inflammatory causes may help broaden the differential diagnosis.

Conclusions

The clinical value of this case lies not merely in reaffirming the non-specificity of tumor markers, but in illustrating a specific extrapelvic differential diagnosis in an appropriate respiratory context. Although elevations of CA19-9 and CA125 have been reported in MPO-ANCA-associated ILD, to the best of our knowledge, reports of this association during long-term surveillance after BOT surgery are limited. Accordingly, when persistent CA19-9 or CA125 elevation occurs despite repeated negative evaluation for BOT recurrence, and is accompanied by respiratory symptoms or fibrotic changes on chest CT, MPO-ANCA-associated ILD should be considered as a possible extrapelvic explanation. More precisely, the tumor marker elevation may have reflected the ILD itself rather than MPO-ANCA positivity. Nevertheless, the association observed in this single case does not establish causality.

Study Approval Statement

The protocol for this study was reviewed and approved by the Institutional Review Board and Ethics Committee of the Japanese Red Cross Ise Hospital.

This study was conducted in accordance with the Declaration of Helsinki and the ethical guidelines established by the ethics committee.

This case report has been prepared in accordance with the CARE guidelines, and the corresponding checklist is provided as supplementary material.

Department and Institution Where Work Was Done

Japanese Red Cross Ise Hospital, 471-2, Funae, Ise, Mie 516-8512, Japan.

Consent for Publication Statement

Written informed consent was obtained from the patient for publication of this case report and accompanying images, in accordance with ethical guidelines.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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