Case Report

Hepatic granulomas heralding eosinophilic granulomatosis with polyangiitis overlapping with Sjögren's syndrome

Running Head: Hepatic granulomas heralding vasculitides

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Abstract

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs) encompass a group of rare autoimmune diseases characterized by granuloma formation and/or inflammation of small vessels. The clinical spectrum of AAV varies widely. Liver involvement is exceptional, posing diagnostic challenges. Moreover, AAV can co-exist with other systemic diseases, further complicating the diagnosis. We herein present a unique case of AAV overlapping with Sjögren's syndrome (SS) with an uncommon onset of the disease.

A 47-year-old female was admitted for hiatal hernia surgery. During the intervention, nodular hepatomegaly was observed. A liver biopsy was performed, showing non-necrotizing epithelioid and central giant cell granulomas. Computed tomography (CT) scan showed perilymphatic pulmonary micronodules with bilateral hilar lymphadenopathies, raising the suspicion of sarcoidosis. Minor salivary gland biopsy revealed Chisholm grade 3 sialadenitis, which, along with the patient's dry eye and mouth symptoms, confirmed SS. Immunological workup showed negative antinuclear antibodies and positive anti-myeloperoxidase (MPO) antibodies. A year later, the patient presented with asthma flare-ups and ear, nose, and throat (ENT) symptoms. A nasal biopsy showed signs of eosinophilic leukocytoclastic vasculitis, confirming the diagnosis of

eosinophilic granulomatosis with polyangiitis (EGPA). Oral steroid therapy was initiated, which resulted in clinical improvement.

We present a case highlighting that EGPA is a protean disease, possibly mimicking or co-occurring with other autoimmune disorders. Thus, it is important to consider the differential diagnoses and carefully monitor for any new symptom or organ dysfunction.

Keywords: ANCA-associated vasculitis; hepatic granuloma; late-onset asthma; leukocytoclastic vasculitis; Sjögren's syndrome.

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are a group of rare autoimmune diseases belonging to the small vessel vasculitis group, according to the Chapel Hill classification, characterized by the formation of granulomas and/or inflammation of small vessels. The clinical spectrum of AAV is large, ranging from benign skin lesions to potentially fatal multisystem dysfunction. The most commonly affected organs are the kidneys, lungs, and peripheral nerves. Yet almost any organ can be affected, often making the diagnosis challenging. Hepatic granulomatosis is an atypical localization during eosinophilic granulomatosis with polyangiitis (EGPA). In addition to its frequently misleading presentations, possibly mimicking other conditions, AAV can co-occur with different systemic diseases, thus further delaying and complicating the diagnosis. Herein, we present a case of an unusual revealing mode of an AAV overlapping with Sjögren's syndrome (SS).

Case Presentation

A 47-year-old female with a history of benign breast tumor resection was admitted to the surgical department for symptomatic hiatal hernia. During the surgery, nodular hepatomegaly was discovered and biopsied. Extemporaneous examination showed non-necrotizing epithelioid and central giant cell granulomas (Fig. 1). Sarcoidosis was suspected; thus, the patient was referred to the internal medicine ward.

Patient interrogation revealed a history of allergic rhinitis and late-onset asthma with frequent flare-ups, treated by bronchodilators and inhaled steroids for over four years. Physical examination revealed papulonodular lesions of the eyelids resembling sarcoid. Blood and urine tests were strictly normal, including liver work-up, inflammation markers, and blood eosinophil count. Tuberculin skin test and liquid mycobacterial cultures were negative.

Chest X-ray showed an apical left lung partially excavated opacity and an interstitial lung pattern. Computed tomography (CT) of the chest, abdomen, and pelvis showed perilymphatic pulmonary micronodules consistent with diffuse interstitial lung disease, a "Galaxy sign" of the left upper lobe, bilateral hilar lymphadenopathies, and an enlarged liver. The total cell count in the bronchoalveolar lavage fluid was slightly higher than normal (250,000 cells per ml), and the CD4/CD8 ratio was 2.3. Spirometry showed a slightly restrictive pattern with a forced expiratory volume in 1 second of 68% and a forced vital capacity of 74%.

In addition to pulmonary symptoms, the patient complained of dry mouth and dry eye sensation, polyarthralgia, and tingling sensation of the feet. The unstimulated whole saliva flow rate and Schirmer's test were both abnormal. A minor salivary gland biopsy was performed and revealed Chisholm grade 3 sialadenitis with no granuloma. Immunologic work-up showed negative antinuclear antibodies and positive perinuclear ANCA (P-ANCA), myeloperoxidase (MPO). Transthoracic echocardiogram and electromyography were normal.

The patient was diagnosed with SS. She was prescribed eye drops and bromhexine. A year later, she presented with epistaxis, and an ENT examination showed a hypertrophied nasal mucosa with multiple ulcerations and signs of nasal obstruction. A nasal biopsy revealed eosinophilic leukocytoclastic vasculitis (Fig. 2).

Maxillofacial CT showed a deviated nasal septum with a left concha bullosa with middle and inferior turbinate swelling and hypertrophy (Fig. 3). Therefore, the diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA) was confirmed according to the 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria. The patient was treated with oral steroid therapy at a dose of 0.5 mg/kg/day. She showed significant clinical improvement with no recurrence of asthma flare-ups.

Discussion

AAVs have witnessed a significant and obvious increase in incidence and prevalence during the last few years, which is most likely explained by a better understanding of the disease and better case definition due to standardized diagnostic criteria. Recent studies, however, have reported a prevalence of 300–421 cases per million persons[1] and an annual incidence of 33 cases per million persons, only four of which are EGPA (12% of all AAVs).[2]

According to a recent US study comparing the incidence and prevalence of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), it is certain that EGPA is the rarest among all AAVs, with an incidence of 0.5–2.3 per 1 million person-years vs. 0.4–11.9 for GPA and 0.5–24 for MPA, and a prevalence of EGPA of 2–22 per million persons vs. 2.9–146 for GPA and 9–94 for MPA.[3]

The mean age of onset of AAVs is reported to be 65 years, with extremes in GPA between 8 and 99 years. According to a Tunisian study, the mean age is 56 years, with extremes between 5 and 72. It is important to mention that the mean age of EGPA onset is generally lower than that in other AAVs. Moreover, patients with ANCA (usually anti-MPO)-positive EGPA are older than those with ANCA-negative EGPA.[3]

For all AAVs, no significant sex difference has been reported, with a sex ratio varying between 1:1 and 1.9:1. For EGPA, however, the sex ratio was 6:1 in a Latin American study. In contrast, males had higher disease activity in EGPA.[3]

ANCA-activated neutrophils release autoantigens from vulnerable microvascular beds and present them to antigen-presenting cells. These autoantigens are recognized by effector T cells, thus causing further injury.

As for EGPA, pathogenesis is substantially different from that of GPA and MPA. EGPA can be ANCA negative; in this case, it is the role of the genes affecting the barrier function and causing mucosal dysfunction. Lyons et al.[4] reported 11 loci associated with EGPA, influencing eosinophil count and underlying asthma. In this case, interleukin 5 (IL-5) is the main cytokine involved, and serum IL-5 levels may be increased. As for ANCA-positive EGPA, it is an eosinophilic autoimmune disease similar to other AAVs, but a direct relationship between anti-MPO and eosinophils has not yet been demonstrated.

The clinical spectrum of EGPA varies widely, but it typically involves the upper and lower respiratory tract, manifesting as nasal polyps, chronic sinusitis, allergic rhinitis, and late-onset asthma. EGPA-related asthma is typically resistant to inhaled steroids and necessitates continuous use of oral corticosteroids, which may have severe side effects. Other respiratory manifestations include pulmonary nodules, interstitial lung disease, and pleural effusion, further underlying the importance of chest CT in diagnosing and monitoring disease activity for prognostic purposes. The second most common organ dysfunction is in the peripheral nervous system, which is polyneuropathy or mononeuritis multiplex, which can be severe.

As supported by the literature, the liver is not typically one of the target organs of AAV. Hepatic involvement in AAV is more associated with GPA than with MPA or EGPA and ranges from asymptomatic elevation of liver enzymes and subclinical liver fibrosis to severe events such as acute or necrotizing hepatitis, hepatic thrombosis, hepatic aneurysms potentially responsible for hemorrhagic shock, and fatal hepatic encephalopathy.[5]

There have been rare reports of hepatic granulomas associated with AAV, most of which are about GPA. Shah et al.[6] reported a case of post-mortem diagnosis of GPA based on the presence of “perivascular and periportal non-caseating granuloma with multinucleated and Langhans' type giant cells” and “necrotizing vasculitis of a small vein” in a liver pathology at autopsy. Grigoriou et al.[7] reported a case of a 22-year-old female with a history of asthma presenting with severe abdominal pain and vomiting, elevated transaminases, positive ANCA antibodies, patchy areas of liver attenuation on CT, and liver biopsy consistent with EGPA. Darnall et al.[8] reported a case of a 66-year-old female with a history of EGPA who presented with abdominal fullness and lower limb edema, liver cirrhosis on CT angiography, and liver biopsy revealing granulomatous formation, eosinophilic infiltration, and vasculitis.

Gastrointestinal manifestations are very rare in EGPA. They are due to eosinophilic infiltration and may vary from abdominal pain to severe intestinal hemorrhage, obstruction, or perforation.

SS is a connective tissue disorder that frequently overlaps with other connective tissue disorders, notably rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and systemic scleroderma (SSc). On the other hand, it rarely overlaps with vasculitis such as AAV. The 44 cases of overlapping AAV and primary SS (pSS) reported in the literature showed that, in addition to the possible positivity of ANCA antibodies in SS, authentic AAV may occur in patients with pSS. Most cases had positive p-ANCA with anti-MPO specificity, and the vast majority presented with SS previously or concomitantly with AAV, as was the case with our patient.

Bilateral hilar lymphadenopathies are typically associated with infections and malignancies. When these are ruled out, sarcoidosis is the most likely diagnosis, especially when biopsy reveals non-caseating granulomas, as was the case with our patient. Although the co-existence of all three diseases seems very unlikely, we found one similar Japanese case reported by Tsuji et al.[9]. AAV and SS are among the rare causes of hilar lymphadenopathies. In this situation, particular attention should be paid to patients with SS because they are at a higher risk of lymphoma.

Morbidity and mortality rates in patients with EGPA are related to the severity of respiratory and cardiac manifestations. However, in this study, we aimed to assess the prognosis of patients with hepatic lesions. As mentioned, hepatic manifestations in AAVs vary widely, from asymptomatic hepatic granuloma or liver function test (LFT) abnormalities to liver fibrosis and fulminant hepatitis. Studies showed that increased gamma-GT values were correlated with an increased disease activity score and were more associated with pulmonary and renal involvement and a longer time to remission, but data are limited to patients with GPA. Classical oral corticosteroid treatment alone relieved the symptoms of our patient.

Based on this case and according to the literature, it seems that asthma in ANCA-positive EGPA is less severe than that in seronegative EGPA. In the latter case, mepolizumab (anti-IL5 monoclonal antibody) seems to be the most effective treatment. Hepatic involvement can present with various clinical manifestations. It may be completely asymptomatic, as in our patient, associated with abnormalities in LFTs, or manifest as a severe presentation with hepatocellular failure.[5]

Conclusion

Initial presentation can be strongly misleading, as was the case with our patient whose liver biopsy and chest CT scan indicated sarcoidosis. However, even with a positive ANCA antibody titer, we could not confirm the diagnosis of EGPA until the patient developed other, more typical disease manifestations. Therefore, it is crucial to consider all the differential diagnoses and to closely monitor key symptoms. If such symptoms emerge, physicians may need to reassess the diagnosis and consequently the therapeutic options, especially when a vital organ is involved.

Our observation highlighted a rare mode of presentation of EGPA and encourages clinicians to consider this diagnosis when faced with hepatic granulomatosis. It allowed us to address the difficulty of establishing the etiological diagnosis in the case of granulomatosis, given the variety of possible diagnoses. Association of a connective tissue disease (such as Sjögren's syndrome) and a vasculitis is possible, as in our case.

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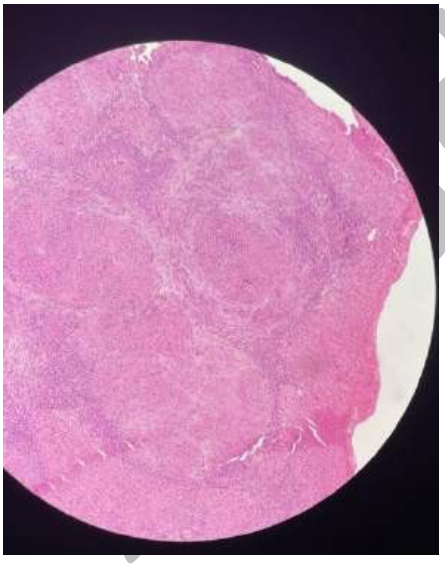

Figure 1. Extemporaneous examination showed non-necrotizing epithelioid and central giant cell granulomas

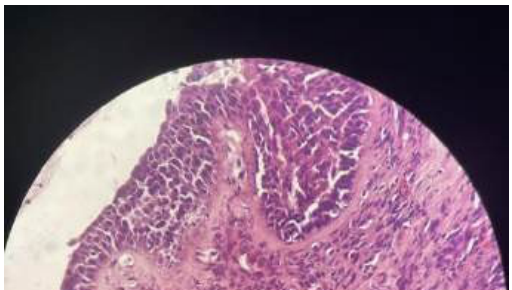

Figure 2. Nasal biopsy revealed eosinophilic leukocytoclast

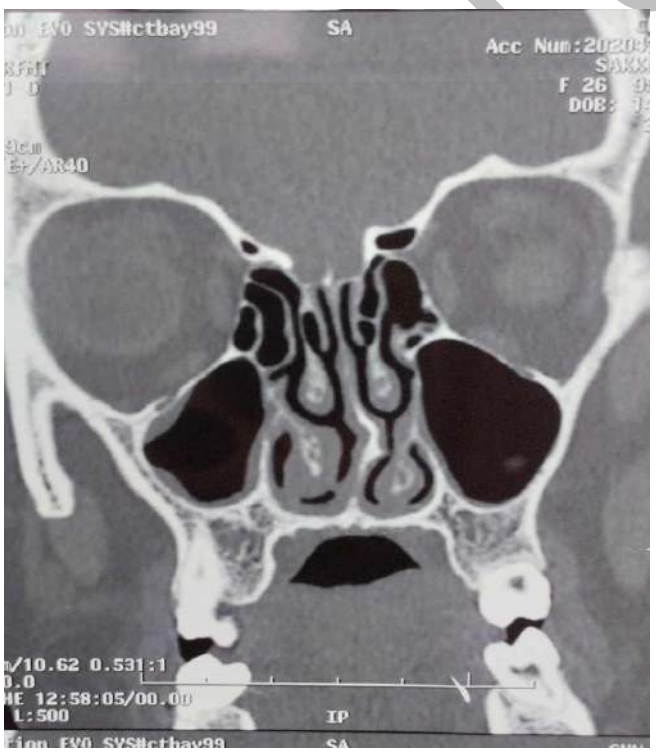

Figure 3. Maxillofacial computed tomography showed a deviated nasal septum with a left concha bullosa with middle and inferior turbinate swelling and hypertrophy