SPLENIC INFARCTION MAY BE THE FIRST SIGN OF GRANULOMATOSIS WITH POLYANGIITIS: CASE REPORTS

Received: March 21, 2024
Accepted: May 24, 2024

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Abstract
Granulomatous polyangiitis (GPA) is a rare systemic vasculitis that makes up most of the antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis (AAV). The disease is more likely to affect the upper and lower respiratory tract, kidney and skin. The gastrointestinal tract involvement is more rare. In the general population, spleen infarction is a rare condition. Most spleen infarcts are asymptomatic, and most patients receive a diagnosis by chance during the evaluation. The most common causes of non-traumatic spleen infarction in the general population include cardiac causes such as atrial fibrillation, infections, thrombophilic conditions, and malignancies. In rheumatic diseases, various spleen involvement has been identified, such as splenomegaly, spleen rupture, spleen abscess, asplenia and spleen infarction. The development of spleen infarct in antiphospholipid syndrome (APS) and systemic lupus erythematosus (SLE) is well known. It is not well known whether GPA is a risk factor for spleen infarction. However, publications including cases of developing spleen infarction due to GPA are increasing. This review highlights the occurrence of spleen infarction in patients with GPA, by presenting two GPA cases with splenic infarction. It also emphasizes that spleen infarction can occur in GPA and may frequently be without symptoms.

Keywords: Splenic infarction, Granulomatosis with polyangiitis, Rheumatology

INTRODUCTION
Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAVs) are rare, primary systemic necrotizing small vessel vasculitis. Systemic AAVs consist of granulomatous– polyangiitis, (GPA) microscopic polyangiitis (MPA) and eosinophilic granulomatous polyangiitis (EGPA). In patients with GPA, the upper respiratory tract, lungs, kidneys and skin are the most frequently involved organs. In GPA, abdominal pain due to gastrointestinal vasculitis, vomiting, bloody diarrhoea, gastrointestinal perforation is expected, while the involvement of other abdominal organs is rare [1].

An infarction of the spleen is a relatively rare condition. Most spleen infarcts are asymptomatic. Most are diagnosed during incidental evaluation. There are not
many studies on the causes of non-traumatic spleen infarct. One study identified atrial fibrillation and other cardiac causes as the most common causes [2]. Another study has been detected malignancies as the most common causes of acute spleen infarction and systemic diseases at a rate of 5% [systemic lupus erythematosus (SLE), sickle cell anemia, and vasculitis] [3]. Infections have also been found to be a major cause [4]. In rheumatic diseases, spleen involvement can be seen in various ways. Spleen rupture, spleen infarction, spleen abscess, splenomegaly, and asplenia have been identified in a variety of rheumatic diseases [5]. Publications involving GPA-related spleen infarction cases are increasing [6-17]. In the literature, spleen infarction has also been identified in patients with MPA and EGPA [18,19]. A series of cases recently evaluating spleen infarction in patients with AAV has also been published [20].

With this report, our aim is to raise awareness of this clinical condition, which can be overlooked among rheumatologists and related physicians, noting that GPA can cause spleen infarction and this condition can be asymptomatic.

**Case 1.**
The 44-year-old female patient was admitted to our rheumatology department at the university hospital due to elevated levels of acute-phase reactants. Laboratory tests were as follows: erythrocyte sedimentation rate (ESR): 94 mm/hour, CRP: 17 mg/dL, and positive c-ANCA test. Spleen infarction material was re-evaluated in our centre. Fibrosis tissue increase was detected in the spleen capsule and small necrosis areas and conjugated vein structures were determined. In the red pulp, fibrinoid necrosis has been seen on the walls of some of the spleen arteries. Several trabecular arteries were dilated and vasculitis was observed in their environment and lumens, characterized by lymphocyte and polymorphonuclear leukocyte infiltration. The patient was accepted as GPA with clinical (splenic vasculitis, upper respiratory tract involvement, polyarthritis) and serological (c-ANCA positivity) findings. Pulse IV methylprednisolone (1 g daily for 3 days) and per oral cyclophosphamide (100 mg/day) were given. The patient's acute phase responses came to normal, his symptoms regressed. In 2012, the patient was diagnosed with intra-abdominal panniculitis and azathioprine was started. The patient was followed for a long time by small doses of steroids and azathioprine. The patient's laboratory tests, which were last evaluated in December 2023, were normal and he was asymptomatic.

**DISCUSSION**
Most rheumatic diseases are characterized by systemic involvement. Like many other organs, the spleen is among the organs that can be affected. The best-known form of spleen involvement is splenomegaly. In addition, spleen rupture, spleen infarction, spleen abscess, asplenia and splenic atrophy are other forms of spleen involvement that can be seen in various rheumatic diseases [5]. An infarction of the spleen is a rare condition. There are not many studies on spleen infarction. Most of the articles in the literature are case reports. The case series is limited. The causes of
spleen infarction in the general population have been investigated in different groups. A retrospective evaluation of patients admitted to the emergency room examined 48 patients who developed a spleen infarction. 10% of patients had splenomegaly, while the most common predisposing factor was atrial fibrillation with 23%. Other causes included bacterial endocarditis, Epstein-Barr virus (EBV) infection, and thrombophilic conditions [2]. In another study, in which 123 patients were analysed and acute spleen infarction was evaluated in imaging, active malignancy was detected in 33% of patients. In 5% of patients, the cause of acute spleen infarction has been linked to systemic diseases. As the cause of the spleen infarction, sickle cell anemia was detected in two patients, SLE in 2 patients and vasculitis in 2 other patients (proven by biopsy) [3]. In a systematic review of spleen infarction, analysis of patients with 18 spleen infarction revealed cancer in 6 patients (33.3%), atrial fibrillation in 4 (22.2%), infection in 4 (22.2%), and 4 (22.2%) other reasons. In this review, from 1975 to 2022, 466 cases were evaluated. In this review, diseases that cause spleen infarction: infection; cancers including myeloproliferative diseases; abnormal blood red sphere (RBC) diseases (sickle cell disease, hereditary spherocytosis), abnormal haemoglobin (haemoglobin SE, β-thalassemia), clotting abnormality (protein C deficiency, protein S deficiency, and antiphospholipid syndrome); vasculitis; and cardiovascular diseases involving atrial fibrillation were divided into 5 groups. The most common causes were infection with 49.1% (229/466) and malignancy with 19.7% (92/466), and vasculitis with 5.1% (24/466) [4]. When the three studies about the causes of spleen infarction abovementioned are examined, it is seen that the etiological causes and patient characteristics vary according to the population, centre and section where the study is conducted. There are no studies in the literature that only investigate spleen infarction in rheumatic diseases. When viewed as a general population, thrombophilic causes rank first among the most important causes of non-traumatic spleen infarction. Infections, including COVID, rheumatic diseases such as antiphospholipid syndrome (APS) and SLE, and vasculitis such as GPA are other causes [4]. In patients with GPA, although rare, the spleen is one of the organs that will be affected. In GPA, the spleen is afflicted affected in different ways. To date, many spleen pathologies have been identified in GPA, such as splenomegaly, capsular adhesion, and infarction [5, 20]. Publications about spleen in GPA were mostly case reports, while a retrospective case series was published [20].

The frequency of spleen involvement in patients with AAV is not known. Most of them are detected incidentally. There is no clear data on the frequency of GPA-related spleen infarction. But increasingly, case reports and case series suggest that spleen infarction is not uncommon in GPA. In fact, according to some studies, spleen infarction in AAVs is not very common except GPA. In a retrospective study of 69 AAV (38 patients with GPA), spleen infarction was found to be 10% in the entire AAV group [20].

Symptoms in an infarction of the spleen are variable. In most of the spleen infarcts detected in GPA, patients are asymptomatic. By chance, they are detected during abdominal computed tomography images [8, 20]. However, as with one of our patients, spleen infarction can be diagnosed with left side pain. Spleen infarction may be the initial sign of GPA or it may occur during follow-up or even while the patient is under immunosuppressive treatment. It appears to occur in most patients during the period when GPA is active [6,7,11,20]. Again, when the cases are examined, it is seen that the proteinase 3 (PR3)-ANCA/c-ANCA antibody is positive in the patients. In the study, which evaluated 38 GPA patients, PR3-ANCA/c-ANCA positive was found in all 7 patients (10%) who developed spleen infarction and kidney involvement was determined in all of them. In this study, which evaluates the risk factors for spleen infarction in GPA, ear nose throat (ENT) and eye involvement were found to be significantly higher in patients with spleen infarction. However, no association was found with sex and acute phase reactants [20].

It is not clear why spleen infarction occurs in GPA patients. In patients with GPA, infarcts are not only seen in the spleen. In the literature, infarcts in multiple organs such as renal infarct and cerebral ischemia are also identified with spleen infarction [9, 11]. It is not known exactly whether infarction-ischemia is caused by vasculitis or by the vasculitis-related hypercoagulable condition. As we mentioned above, most cases have developed spleen infarction in terms of GPA during the active period and again most patients are PR3-ANCA/c-ANCA positive. It has been suggested that active disease and PR3-ANCA/c-ANCA lead to a hypercoagulable condition [16,17]. According to some authors, the spleen is more prone to infarction as a result of blockage of distal splenic arteries, arterioles and collateral, and in GPA, this is due to blockage of distal parenchymal splenic arteries [8]. Signs of vasculitis (fibrinoid necrosis, necrotizing arteritis) have also been shown in histopathological examinations of patients with GPA [5].

In our patient (case 2), who
underwent splenectomy, splenic material re-examined showed vasculitic changes involving fibrinoid necrosis. This made us think that the infarction is due to vasculitis.

As a result, vasculitis, especially GPA from AAVs, appears to be a major cause of spleen infarction. Even if asymptomatic, GPA patients should be investigated and monitored for possible silent spleen infarction. Additionally, general practitioners and rheumatologists should also evaluate the patients with splenic infarction for possible GPA. Although spleen infarction has been shown to develop in GPA, information on its frequency, possible risk factors is not clear. Information on etiopathogenesis is also limited. Prospective and wide-ranging studies are needed to determine the frequency and possible risk factors for developing spleen infarction in GPA patients and other vasculitides.

AUTHOR CONTRIBUTIONS
All authors substantively contributed to the drafting of the initial and revised versions of this review. They take full responsibility for the integrity of all aspects of the work.

CONFLICTS OF INTERESTS
All authors have completed the ICMJE Disclosure Form (http://www.icmje.org/disclosure-of-interest; available on request from the corresponding author). All authors declare that there are no potential conflicts of interest.

INFORMED CONSENT
Written informed consent was obtained from the patients for publication of this case report.

DISCLAIMER
No part of this review is copied or published elsewhere in whole or in part.

References

Құқыбауыр инфарктісі поліангітіт кезінде грануломатоздың алғашқы бөлісі болуы мүмкін: Сырқаттама

Түйіндеуеме
Грануломатозды поліангітіт (ГРА) - сирек кезедегің жұйелік васкуліт, ол антинейтрофілді цитоплазмалық антидепілермен (АНЦА) байланысты васкуліттің қоң бөлігін құрайды. Ауру қобінесе жогарғы және төменгі тыңыс жолдрарына, буйыркегерге және теріге асер етеді. Асканаз-ішек жолдарының зақымдануы сирек кезедесі. Жалпы популяцияда құқыбауыр инфарктісі сирек кезедетін ауру болып табылады. Құқыбауыр инфарктісінің көбісі асімптоматықтар түрде өтіп, пациенттердің қошшылығына тексеру кезінде кездейсқұ дайындық қойылады. Жалпы популяциядағы жаракаты құқыбауыр инфарктісінің ең қоң таражан себептеріне жүргізеді. Фибринолізіясы, инфекциялар, тромбофіліді жәндайылар және қатерлі ісіктер сияқты жүрек септемтері жатады.

Ревматологиялық ауруларда спленомегалія, құқыбауырдің жарылуы, құқыбауырдың абсцезсі, асплена және құқыбауыр инфарктісі сияқты құқыбауырдың артурлі зақымдануы анықталады.

Антифосфоліпрінді синдром (АФС) және жұйелі қызык жегі (SLE) кезінде құқыбауыр инфарктісінің дамуың бәрі болды, ГРА құқыбауыр инфарктісінің қауіп факторы екені беғісіз. Алайда, ГРА салдарынан құқыбауыр инфарктісінің даму жаңдайларының қамтылық жағынанымдар саны артып келеді. Бул шоюда құқыбауыр инфарктісімен ауыратын науқастарда құқыбауыр инфарктісінің туынды тұралы қарап, бұл құқыбауыр инфарктісі бар ГПА-ның екі жаңдайының білімдірі. Ол сондай-ақ құқыбауыр инфарктісі ГПА кезінде пайдасы болуы мүмкін және қандаи дә бір беғісіз жүргі мүмкін.

Түйінде сәлдәр: құқыбауыр инфарктісі, поліангітітпен грануломатоз, ревматология.

Дойексөз үшін: Ускюдар Джансу Д, Йылдырим Р, Коркмаз К. Құқыбауыр инфарктісі поліангітіт кезінде грануломатоздық ағашқаты болуы мүмкін: сырқаттама. Орталық Азиялық медицина гипотезасы мен әдіс-қарастары, жылылық 2024:5(2):93-98, https://doi.org/10.47316/cajmhe.2024.5.2.02

Инфаркт селезенки може быть первым признаком гранулематоза при полиангитите: история болезни

Резюме
Гранулематозный поліангітіт (ГПА) — редкий системный васкулит, который составляет большую часть васкулита, ассоциированного с антинейтрофильными цитоплазматическими антителами (АНЦА). Заболевание чаще поражает верхние и нижние дыхательные пути, почки и кожу. Поражение желудочно-кишечного тракта встречается реже. В общей популяции инфаркт селезенки является редким заболеванием. Большинство инфарктов селезенки протекают бессимптомно, и больницею пациентов диагноз ставится случайно во время обследования. Наиболее распространённые причины нетравматического инфаркта селезенки в общей популяции включают сердечные причины, такие как фибрилляция предсердий, инфекции, тромбофиллические состояния и люкокластические новообразования. При ревматических заболеваниях выявляют различные поражения селезенки, такие как спленомегалия, разрыв селезенки, абсцесс селезенки, асплена и инфаркт селезенки. Развитие инфаркта селезенки при антифосфолипидном синдроме (АФС) и системной красной волчанке (СКВ) хорошо известно. Неназнается, является ли ГРА фактором риска инфаркта селезенки. Однако количество публикаций, включающих случаи развития инфаркта селезенки вследствие ГПА, увеличивается. В этом обзоре освещается возникновение инфаркта селезенки у пациентов с ГПА, представляя два случая ГПА с инфарктом селезенки. В нем также подчеркивается, что инфаркт селезенки может возникать при ГПА и часто протекать без симптомов.

Ключевые слова: инфаркт селезенки, гранулематоз с полиангитом, ревматология.

Для цитирования: Ускюдар Джансу Д, Йылдырим Р, Коркмаз К. Инфаркт селезенки как первый признак гранулематоза при полиангите: история болезни. Центральноазиатский журнал медицинских гипотез и этики 2024:5(2):93-98. https://doi.org/10.47316/cajmhe.2024.5.2.02