Received: 22 November 2023 | Accepted: 21 December 2023

DOI: 10.1002/jha2.848

eJHaem

British Society for Haematology

CASE REPORT

Autoimmune thrombotic thrombocytopenic purpura associated with disseminated sarcoidosis: A case report

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Abstract

Sarcoidosis is an inflammatory disease known to be associated with multiple autoimmune disorders. There is a restricted number of descriptions of the association between sarcoidosis and autoimmune thrombotic thrombocytopenic purpura (aTTP). We present the case of a 63-year-old woman admitted to the hospital to investigate a possible sarcoidosis who had hemolytic anemia and thrombocytopenia, with low ADAMTS13 activity and anti-ADAMTS13 antibodies, leading to a diagnosis of aTTP. Sarcoidosis was later confirmed and the two conditions evolved separately after 6 months, questioning the link between them. Clinicians should be aware of this rare cause of thrombocytopenia in patients with sarcoidosis, as aTTP is a life-threatening condition.

KEYWORDS
ADAMTS13 antibodies, case report, sarcoidosis, thrombotic thrombocytopenic purpura

1 | INTRODUCTION

Sarcoidosis is a T-cell-mediated condition with a non-necrotizing granulomatous reaction, known to be associated with multiple autoimmune disorders. Autoimmune thrombotic thrombocytopenic purpura (aTTP) is a rare disease, defined by a severe decrease in the activity of von Willebrand factor-cleaving protease ADAMTS13, caused by the presence of inhibitory antibodies. It is characterized by thrombocytopenia, microangiopathic hemolytic anemia, and sometimes organ damage. Association between sarcoidosis and aTTP was rarely reported. We present a case of a patient who developed aTTP during investigations of mediastinal lymphadenopathy leading to a diagnosis of sarcoidosis.

2 | CASE REPORT

A 63-year-old woman with a medical history of psoriasis treated for 8 years with topical steroids, was first seen by a pneumologist for a chronic cough for at least 3 years with obstructive disorder at pulmonary function tests (PFTs). Chest CT scan showed diffuse bilateral micronodular infiltrates with perilymphatic distribution, and bilateral mediastinal and hilar lymphadenopathy, suggesting sarcoidosis. Flexible bronchoscopy with bronchial biopsies was performed, without abnormalities. Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) showed disseminated hypermetabolic lymphadenopathy associated with multiple hypermetabolic lesions of both lungs, spleen, liver, and bones (Figure 1).

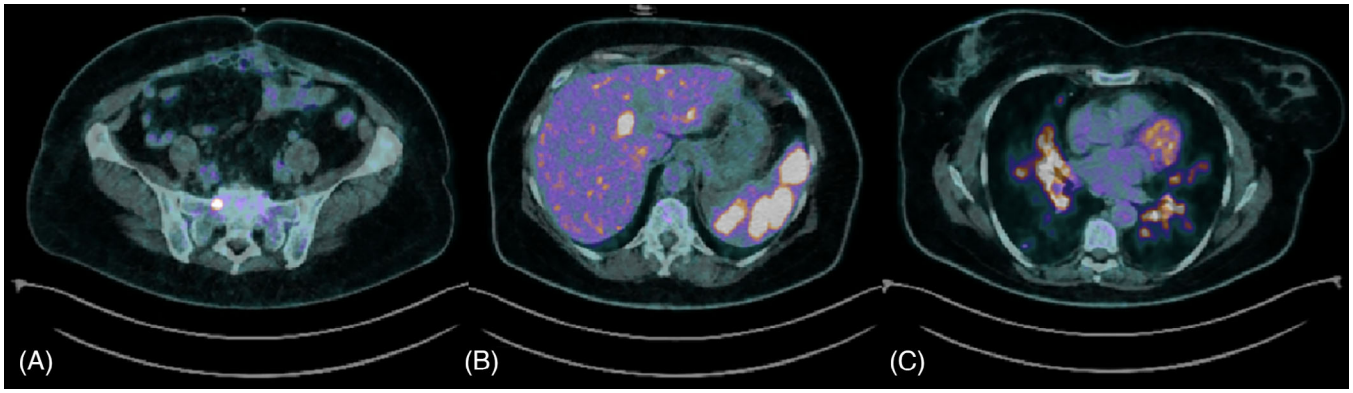

FIGURE 1 Initial Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) showing hypermetabolic lesions of bones (A), liver, spleen (B), and hypermetabolic mediastinal lymphadenopathy (C).

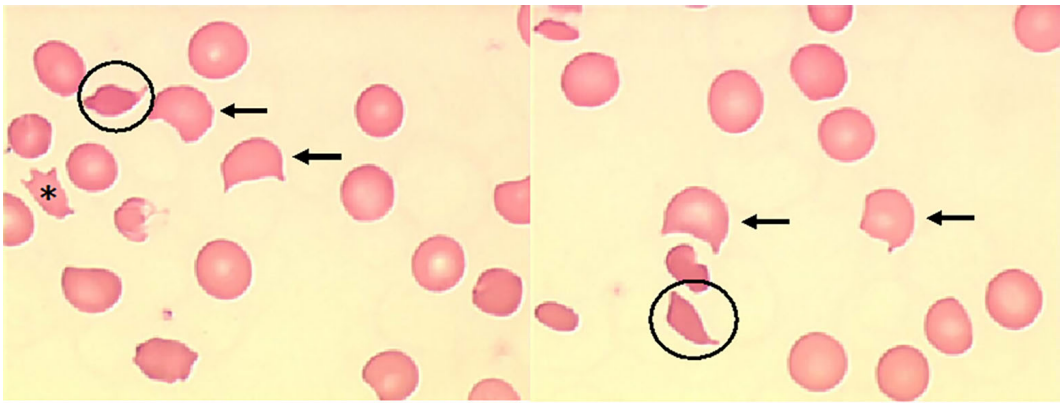

FIGURE 2 Peripheral blood smear with helmet-shaped (arrows), comma-shaped (circles), or triangular (star) schistocytes.

The patient was referred to the internal medicine department for further exploration. Physical examination was normal. Blood samples revealed unexpected results: hemolytic anemia with reduced hemoglobin (10.4 g/dL), high reticulocyte count (283 G/L), undetectable haptoglobin concentration (< 0.02 g/L), and an elevated lactate dehydrogenase level (648 UI/L), associated with thrombocytopenia (27 G/L). Schistocytes were observed on the peripheral blood smear (1.8%) (Figure 2). Coagulation parameters and renal testing were normal. PLASMIC score was 6, corresponding to a high risk of thrombotic thrombocytopenic purpura. She was promptly transferred to the intensive care unit to start plasma exchange (PE), steroids (pulsed intravenous methylprednisolone followed by prednisone 1 mg/kg/d), and four infusions of rituximab 375 mg/m^2 in 15 days. The former hypothesis was later confirmed, with severe deficiency of ADAMTS13 activity (< 5%), and positive anti-ADAMTS13 IgG (51 U/mL, positive > 25 U/mL). Platelet level returned to normal after 7 days of PE but decreased again contrasting with normalization of hemolysis parameters (haptoglobin at day 4, reticulocytes at day 14, and schistocytes at day 17) and ADAMTS13 activity (89% at day 14) (Figure 3). PE could be stopped after 30 days. The patient remained clinically stable during the whole PE period.

Further evaluation was performed to support the diagnosis of sarcoidosis. Blood tests demonstrated a constant lymphopenia around 0.8 G/L (prior to TTP) and a slight increase of angiotensin-converting enzyme (71 UECA, normal value < 70 UECA). Wedge resection of the upper lobe of the left lung found nodular structures in the subpleural area and around bronchioles. These nodules were composed of a hyaline collagenous center with peripheric giant cell granulomas. Round inclusions with a 4 μm diameter were seen, reacting with PAS, Grocott, and Ziehl colorations, suggestive of Hamazaki-Wesenberg bodies (Figure 4).

Steroids were gradually reduced. After 6 months, the patient received prednisone 10 mg/d and ^{18}F-FDG PET/CT showed a partial metabolic and morphological response in lymphadenopathy and metabolic regression of other lesions (Figure 5). PFT improved and there was no reason to start immunosuppressive therapy. ADAMTS13 activity monitoring revealed a fall below 20% at 6 months with no

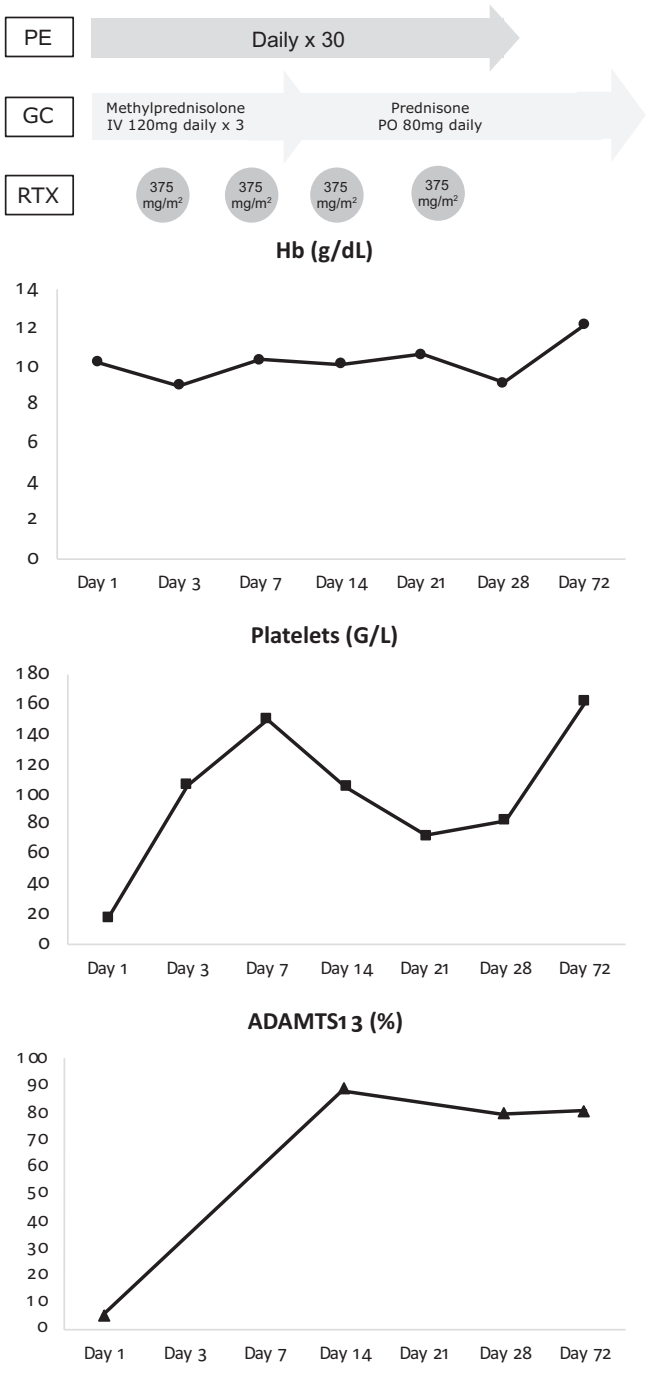

FIGURE 3 Laboratory follow-up during 2 months after treatment initiation with daily plasma exchange (PE), glucocorticoids (GC), intravenously (IV) with methylprednisolone then per os (PO) with prednisone, and rituximab (RTX) 4 infusions of 375 mg/m^2 within 15 days.

clinical signs nor blood test abnormalities. A pre-emptive therapy with rituximab was given and ADAMTS13 activity quickly returned to normal. After 18 months, aTTP and sarcoidosis were considered to be in remission.

3 | DISCUSSION

aTTP is a rare condition with the production of autoantibodies against ADAMTS13. This metalloprotease normally cleaves multimers of the von Willebrand factor. In the absence of this inhibitor, platelets are activated and aggregate in microcirculation, contributing to multiple organ failure, such as neurological disorders or acute kidney injury. There is a mechanical lysis of erythrocytes against these microthrombi [1]. An association of thrombocytopenia and hemolytic anemia with schistocytes should alert clinicians, as this affection has a high mortality rate without treatment. Current therapies combining PE, steroids, rituximab, and caplacizumab, have greatly improved its prognosis [2].

aTTP can be associated with infection (e.g., HIV), pregnancy, cancer, or autoimmune disorder [3]. Association with systemic lupus erythematosus (SLE), Sjogren's syndrome (SS), or autoimmune thyroiditis (AIT) is the most widely described [4].

Sarcoidosis is a T-cell-mediated condition with a non-necrotizing granulomatous reaction, known to be associated with an autoimmune disorder in 11.5%–17.6% of patients [5–7]. In the Taiwanese population, Wu et al. found a significant association between sarcoidosis and AIT (11.6%), ankylosing spondylitis (AS, 3.64%), and SS (1.54%) [7]. Brito-Zerón et al. studied a Spanish cohort of 1737 patients with sarcoidosis: main comorbidities were AIT (5.4%), SS (1.7%), psoriasis (1.6%), and AS (0.7%) [5]. Statistical significance was reached for SS and AS. Nine patients suffered from immune thrombocytopenia, and a single patient had thrombotic microangiopathy, without more details. Rajoriya et al. found, in a cohort of 1510 British patients, a strong association between sarcoidosis and SLE, and autoimmune hepatitis [8].

Only three articles reported aTTP associated with sarcoidosis [9–11]. We compare them to our recent case in Table 1. We did not find any details of whether or not the two conditions developed separately. In our patient's case, sarcoidosis lesions regressed while at the same time, ADAMTS13 activity fell again, calling into question the strength of the association between the two conditions.

In clinical practice, aetiological diagnosis of thrombocytopenia discovered in sarcoidosis is challenging. There are three main causes of this: hypersplenism [12], bone marrow infiltration [13], and immune thrombocytopenic purpura [14]. Thrombotic microangiopathy can be discussed, with normal ADAMTS13 level as described by others [15] or with low ADAMTS13 activity as in these presented cases.

4 | CONCLUSION

Association between sarcoidosis and aTTP is rare. In our case, the diagnosis of these two conditions was simultaneous. Their dissociated evolution provides an answer to the question of the link between them. In clinical practice, this case highlights the need to discuss the diagnosis of thrombotic microangiopathy when faced with hemolytic anemia associated with thrombocytopenia, as it is a medical emergency with a good prognosis if rapidly treated.

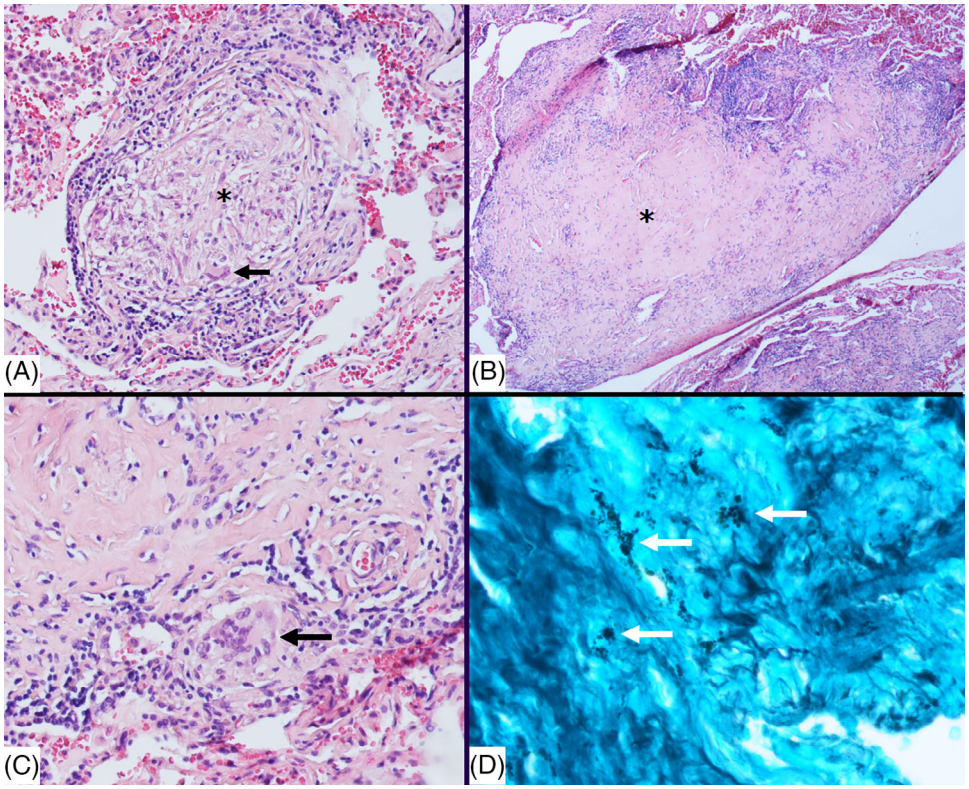

FIGURE 4 Histology of the wedge resection of the upper lobe of the left lung. (A) Granuloma (star) with giant cell (arrow). (B) Hyaline collagenous center of a granuloma (star), occurring in the late stage of sarcoidosis. (C) Focus on a giant cell (arrow). (D) Grocott-tainted inclusions corresponding to Hamazaki-Wesenberg bodies (arrows).

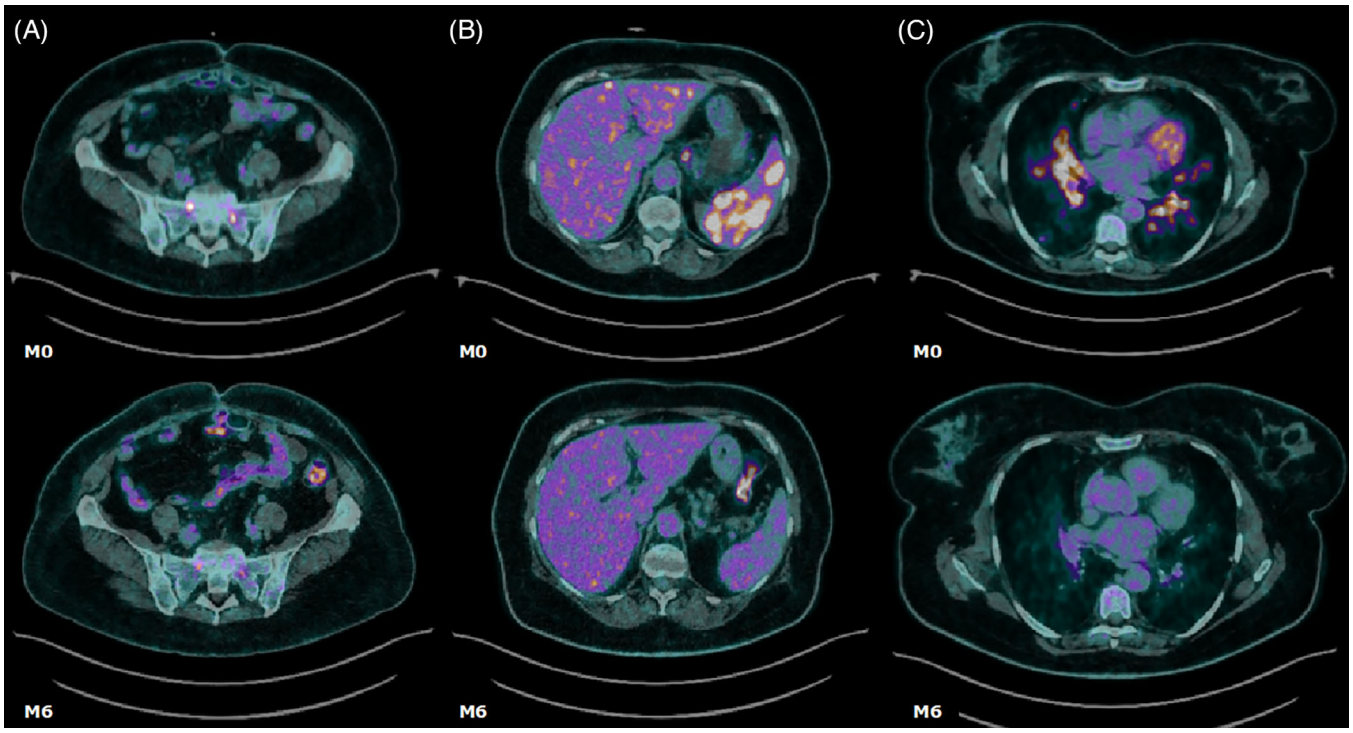

FIGURE 5 Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) after 6 months showed metabolic regression of bones (A) and liver and spleen lesions (B), and partial metabolic and morphological response in mediastinal lymphadenopathy (C).

TABLE 1 Comparison of data from the three cases already reported [9–11] and our case.

		Reference			
Patient's data		[9]	[10]	[11]	Current case
Sex/Age		H/28	H/32	F/48	F/64
aTTP	Fever	0	Yes	Yes	0
	Bleeding	0	Yes	0	0
	Hemoglobin	NA	9	6.4	10.2
	Platelets	12	30	10	17
	ADAMTS13	NA	<1%	NA	<5%
Sarcoidosis	Pulmonary	Yes	Yes	Yes	Yes
	Lymph nodes	0	Yes	Yes	Yes
	Hepatosplenic	0	0	0	Yes
	Bones	0	0	0	Yes
	Granuloma	Yes	Yes	Yes	Yes
aTTP treatment	PE	Yes	Yes	Yes	Yes
	Steroids	Yes	Yes	0	Yes
	Rituximab	0	Yes	0	Yes
Outcome	Remission	Yes	Yes	Yes	Yes
	Relapse	Yes	0	0	Yes

Abbreviations: aTTP, autoimmune thrombotic thrombocytopenic purpura; NA, not applicable; PE, plasma exchange.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

FUNDING INFORMATION

We have no funding to report for this article.

DATA AVAILABILITY STATEMENT

n/a

ETHICS STATEMENT

The authors have confirmed ethical approval statement is not needed for this submission.

PATIENT CONSENT STATEMENT

We obtained signed permission to publish a case report.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

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How to cite this article: Billotte M, Eszto P, Thomas B, Groizard P, Perez P, Campagne J. Autoimmune thrombotic thrombocytopenic purpura associated with disseminated sarcoidosis: A case report. eJHaem. 2024;5:225–30. https://doi.org/10.1002/jha2.848