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CASE-BASED REVIEW

Refractory Acquired Amegakaryocytic Thrombocytopenia with Rapid Progression to Aplastic Anaemia in SLE

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ABSTRACT

Acquired amegakaryocytic thrombocytopenia (AAMT) is a rare cause of thrombocytopenia seen in systemic lupus erythematosus (SLE) that is frequently misdiagnosed as immune thrombocytopenic purpura (ITP). Often patients do not respond to standard ITP treatment. Prompt bone marrow biopsy and further workup should ensue as it is a diagnosis of exclusion. While no standard guidelines exist, the mainstay of treatment is immunosuppressive therapy. Some cases are refractory and should have a follow-up biopsy, typically showing worsening disease. The exact pathogenesis is unclear; multiple mechanisms may be involved, suggesting AAMT may be a syndrome of various aetiologies rather than a distinct pathology. A common complication is aplastic anaemia, and the patient may need a haematopoietic stem cell transplant (HSCT). We present a young man with severe refractory AAMT in the setting of SLE that progressed to aplastic anaemia and required an HSCT. We then discuss and interpret the literature on AAMT.

INTRODUCTION

Thrombocytopenia is common in systemic lupus erythematosus (SLE). Immune thrombocytopenic purpura (ITP) is the most frequent aetiology and typically responds to corticosteroids and conventional immunosuppressants. Another aetiology, albeit rare, is acquired amegakaryocytic thrombocytopenia (AAMT). It presents similarly to ITP and is frequently misdiagnosed; hence, the incidence is often higher than reported. However, its pathogenesis differs, and bone marrow (BM) biopsy does not show a reactive increase of megakaryocytes. It is refractory to most immunosuppressants, and no standard treatment is available. The clinical course is highly variable and often progresses to aplastic anaemia. Here, we present a case of AAMT in SLE that was refractory to multiple immunosuppressive therapies. Our patient developed aplastic anaemia with transfusion dependence and required a bone marrow transplant (BMT). Early diagnosis of AAMT is crucial when thrombocytopenia is not responsive to standard treatment as these patients may benefit from an early BMT.

Keywords: acquired amegakaryocytic thrombocytopenia, AAMT, lupus thrombocytopenia, bone marrow megakaryocyte hypoplasia, refractory thrombocytopenia, early bone marrow transplant
CASE DESCRIPTION
Written informed consent was obtained from the patient prior to completing this case report. A 28-year-old man presented with two weeks of abrupt onset petechiae. He stated he had not been in contact with anyone who was symptomatic with an infectious illness, had no recent viral illness, was never sexually active, and was not on any medications. He denied haematuria, haematochezia, hair loss, joint pains, oral ulcers, Raynaud’s phenomena, dry eyes, and dry mouth. He had a family history of pernicious anaemia in one sister, pityriasis lichenoides et varioliformis acuta in another, and rheumatoid arthritis in his maternal grandmother. Physical exam revealed petechiae on bilateral forearms but was otherwise unremarkable, with no hepatosplenomegaly or mucosal lesions. Further workup showed severe thrombocytopenia (2.0x10^9/L), anaemia (109 g/L), and leucopenia (3.49x10^9/L). His autoimmune serologies showed positive antinuclear autoantibodies (ANA), double-stranded DNA autoantibodies (anti-dsDNA), Sjögren’s-syndrome-related antigen A/B autoantibodies (anti-SSA/SSB), and DNA extractable nuclear antigen ribonucleoprotein autoantibodies (anti-ENA-RNP). They were negative for anti-Smith autoantibodies (anti-Sm), beta-2-glycoprotein autoantibodies (anti-B2gP), and cardiolipin autoantibodies (anti-cardiolipin). He also had low complement 4 levels. Peripheral smear was negative for schistocytes. There were no peripheral smear or laboratory evidence of haemolysis. He also had a low reticulocyte count. Infectious workup (Ebstein Barr Virus [EBV], cytomegalovirus [CMV], Human Immunodeficiency Virus [HIV], and Hepatitis C Virus [HCV]) was negative. He tested positive for Hepatitis B core antibody, but that was attributed to the IVIG transfusions. Nevertheless, he was started on tenofovir to treat Hepatitis B Virus [HBV]. The working diagnosis at this point was ITP secondary to SLE. While ITP is defined as isolated thrombocytopenia, some patients with lupus can have thrombocytopenia as their only symptom before diagnosis. One study found that patients with an initial diagnosis of ITP who later developed SLE had significantly lower haemoglobin levels/anaemia compared to those who did not develop SLE. Furthermore, SLE is associated with various hematologic abnormalities. Our patient likely had undiagnosed SLE at the time of his presentation, accounting for his pancytopenia rather than isolated thrombocytopenia. Additionally, ITP is the most common aetiology of thrombocytopenia in SLE. The patient was started oral steroids and IVIG. He was also given rescue platelet transfusions for critically low levels (<10x10^9/L). Due to lack of response, a BM biopsy was performed, which revealed hypocellular marrow (30-40% cellularity), no evidence of leukaemia or lymphoma, and severely decreased megakaryocytes. This was suggestive of AAMT. The patient never exhibited any signs of active bleeding. He was given plasma exchange, IV parenteral steroids, and other immunosuppressants, as summarised in Figure 1, but the patient remained thrombocytopenic (platelet count below 30x10^9/L). Of note, cyclophosphamide was offered, but the patient refused due to its side effects. When the patient became leukopenic, we considered medication-induced pancytopenia and hydroxychloroquine, mycophenolate mofetil, cyclosporine, and tenofovir were held in addition to decreasing the methylprednisolone dose. However, the patient continued to be pancytopenic.

A second BM biopsy was performed as the pancytopenia did not improve, and the results showed worsening hypocellular marrow with cellularity to 10-20% with occasional histiocytes showing hemophagocytosis, concerning for hemophagocytic lymphohistiocytosis (HLH). However, the patient did not have clinical or laboratory features of HLH. Serum triglycerides, ferritin, fibrinogen, and serum interleukin two receptor (sIL-2R) were all within normal limits. The diagnosis of AAMT secondary to SLE was maintained. The complicated hospital course is summarised in Figures 1 and 2. The patient was discharged, and we continued to follow him outpatient. Eltrombopag was added to his regimen. He still did not respond to immunosuppressant treatment. He remained platelet transfusion dependent, eventually became blood transfusion dependent due to worsening anaemia, and also developed worsening leukopenia. Still, he never displayed any signs of bleeding. The patient was ultimately referred for BMT for aplastic anaemia, which was diagnosed based on his laboratory blood analysis which confirmed low cell counts in all cell lines in addition to the hypocellularity seen on the second BM biopsy. The patient’s outpatient management course is summarized in Figures 3 and 4.

DISCUSSION
Thrombocytopenia (platelet count <100x10^9/L) can be found in 7-30% of SLE cases. Up to 14% of patients with lupus can have thrombocytopenia as the sole finding for up to 10 years before diagnosis. SLE thrombocytopenia is an independent mortality predictor and is associated with a worse prognosis. Among lupus thrombocytopenia cases, severe thrombocytopenia (platelet count <50x10^9/L) can be seen in 27.9% of them as per a recent Chinese cohort study. That same study demonstrated severe thrombocytopenia to be associated with relatively quiet lupus and decreased survival rate. Our patient presented with isolated severe thrombocytopenia in the setting of asymptomatic, undiagnosed lupus that was refractory to most treatments.

Some of the most common causes of thrombocytopenia in lupus are medications, viral infections (EBV, CMV, HIV, HCV, parvovirus, HBV), antiphospholipid syndrome,
thrombotic microangiopathies, all of which were ruled out in our patient. Other mechanisms are impaired mega-karyocyte production and immune-mediated platelet destruction. The latter is the most common aetiology, which prompted our patient, who had severe thrombocytopenia and positive SLE serologies with a negative workup, to be treated with steroids and IVIG. When his BM biopsy was done due to lack of response after five days, it showed depleted megakaryocytes, making ITP a very unlikely diagnosis. ITP is due to autoantibodies tar-
1  BM biopsy in ITP typically shows normal or increased megakaryocytes, inconsistent with our patient. Our patient’s initial biopsy was done after five days of no response to aggressive immunotherapy for presumed ITP. There is no standardised guideline regarding when to perform a BM biopsy after patients with thrombocytopenia do not respond to initial therapies. Case reports have described performing biopsies any time after three days to five months to possibly years. Therefore, diagnosis, and thus treatment, of AAMT can be delayed when a low platelet count is further investigated. Studies are needed to compare the timeframes of obtaining BM
biopsies in patients presenting with grave thrombocyto-
topenia. An additional point to consider is that mega-
karyocyte counts in the BM may have a predictive value in
determining response to therapy in patients with SLE
who have thrombocytopenia.15 When thrombocytopenia is
persistent and severe, one should not hesitate to re-
peat a BM biopsy. Our patient displayed a worsening BM
response, consistent with other published studies.14–16
In two of these studies, AAMT progressed to aplastic
anemia.15,16 Therefore, repeat biopsy has the potential
to predict clinical outcomes. Furthermore, HLH
should be suspected with unrelenting thrombocytopenia, but
this was deemed unlikely in our case. Although some
hemophagocytic histiocytes were noted on repeat BM
biopsy, he did not fulfill HLH criteria due to the absence
of fever, organomegaly, elevated ferritin, and elevated
sIL-2R.

Our patient’s biopsy was consistent with AAMT.5 AAMT
is a diagnosis of exclusion, and other causes of acquired
thrombocytopenia should be ruled out. For example,
endogenous stimuli can suppress megakaryocyte mat-
uration due to antibody or T-cell-mediated immunity.4,17
AAMT has been associated with systemic lupus ery-
thematosus, eosinophilic fasciitis, systemic sclerosis, and
adult-onset Still’s disease, among other autoimmune
disorders.18–20 Our patient did not have clinical features
of these disorders. Lastly, AAMT has been described as
an early manifestation of a stem cell abnormality, such as
a precursor to acute myeloid leukaemia, myelodysplastic
syndrome, and non-Hodgkin’s lymphoma.2 However,
our patient’s BM biopsies were negative for malignancy.
In our case, we exhausted the various aetiologies of
thrombocytopenia and found that he likely has AAMT
secondary to SLE. While the exact pathogenesis remains
unknown, autoantibodies against thrombopoietin (THPO)
or THPO receptor are thought to be involved.5,14,17,21
The most common antibodies associated with lupus throm-
bocytopenia are anti-Glycoprotein IIa/IIlb and anti-THPO
antibody.4 THPO binds to its receptor and stimulates
megakaryocyte maturation and platelet production.
Antibodies against this cytokine or its receptor inhibit
megakaryopoiesis leading to low or absent megakaryo-
cytes in the BM.4,17 Anti-THPO antibodies are associated
with bone marrow megakaryocytic hypoplasia and poor
response to standard immunosuppressants.4,17 On
the other hand, anti-glycoprotein IIa/IIlb is associated with
peripheral platelet destruction or splenic sequestration,
and associated with high megakaryocyte density
compared to anti-THPO antibodies.

There are several case reports on AAMT but no extensive
studies to investigate the clinical outcomes of this dis-
ese. There are also no randomized clinical trials (RCTs)
for treatment of the disease. Immunosuppression, how-
ever, remains the initial foundation of therapy. The follow-
ing medications and therapies have been used for the
treatment of AAMT:2,3,5,11,14,22,23 steroids (which suppress autoimmunity mediated by B and T cells), IVIG (which
binds antibodies against THPO and megakaryocytes),
plasma exchange (which removes and filters antibodies
from the patient’s plasma), rituximab (which suppresses
autoantibody production by B cells), cyclosporine (which
is a calcineurin inhibitor that suppresses T-cell activation),
anti-thymocyte globulin (which suppresses autoimmunity
mediated by T cells and directly stimulates haematopoi-
esis), cyclophosphamide (which is immunosuppressive),
azathioprine and mycophenolate mofetil (which diminish
immune cell proliferation, especially in patients with
systemic lupus erythematosus), eltrombopag (which sti-
mulates THPO receptor), and BM transplant (which
replaces a patient’s BM, including their megakaryocytes).
A variety of these drugs were tried on our patient. Still,
he progressed to aplastic anaemia that was transfu-
sion-dependent, a known complication of the intense
autoimmune processes of AAMT.9

Before the 2000s, anti-thymocyte globulins (ATG) and
cyclosporine were successfully used to treat AAMT.24,25 One
of the most extensive case series on AAMT by Manoharan
et al. has shown responses to various treatments, and
patients treated with ATG had the best outcomes.26 Few
other case reports have shown a failed response
to ATG but a good response to cyclophosphamide or
cyclosporin.22,24,27 Recent studies have demonstrated
success with rituximab, eltrombopag, romiplostim, and
BMT.11,14,23,28 Eltrombopag was approved for use in pri-
mary ITP, and recently a small RCT showed promising re-
sults with eltrombopag in ITP associated with connective
tissue disorders.29 Nevertheless, there is a paucity in
the literature on the use of any of these treatments in AAMT.
A couple of case reports discuss the response with eltrom-
bopag and romiplostim.25,28 Eltrombopag, specifically,
stimulates THPO receptor at a transmembrane region of
THPO receptor, while THPO binds to the distal portion,
cytokine receptor homologous domain 2, of THPO
to activate megakaryocyte maturation.30 This suggests that
eltrombopag may provide an adequate response in the
presence of anti-THPO receptor antibodies.29 Review
of our patient’s case in combination with other cases in the
literature suggests that AAMT may describe a syndrome
secondary to various mechanisms rather than a discrete
disease with a defined pathogenic process. Further
research is needed to elucidate the pathogenesis and
treatment of this disease.

The prognosis for AAMT varies from immediate remission
after therapy to a long relapsing-remitting course to pro-
gression to aplastic anaemia in 1 month to 2 years.5,15,21,22
Our patient rapidly progressed to aplastic anaemia in a
span of two weeks. However, once aplastic anaemia has
occurred, the prognosis is poor. Patients may require a
haematopoietic stem cell transplant (HSCT) to achieve
remission.11 HSCT cases have shown increased survival

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in congenital amegakaryocytic thrombocytopenia. Early HSCT may also be beneficial in AAMT; to the best of our knowledge, two case reports show favourable outcomes with HSCT in patients with AAMT.11,21

CONCLUSION
AAMT is one of the uncommon haematological manifestations of lupus. It is underrecognised and underdiagnosed as most thrombocytopenia in SLE is assumed to be ITP. Although ITP is the most common cause of thrombocytopenia in SLE, a suspicion of AAMT is essential, and prompt BM biopsy should be obtained, especially when there is no response to standard steroids and IVIG. Biopsy shows low or absent megakaryocytes. Refractory AAMT in a young patient should be treated aggressively, and repeat BM biopsy may sometimes be essential when there is no response to standard immunosuppression. Furthermore, early referral to HSCT may be the next logical step.

CONFLICT OF INTEREST
None.

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DISCLOSURES
None. All co-authors take full responsibility for the integrity and accuracy of all aspects of the work.

REFERENCES


**THROMBOCYTOPENIA IN SLE MAY NOT ALWAYS BE ITP**