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CASE REPORT

Aplastic anemia associated with systemic lupus erythematosus in children – case report and review of the literature

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Key Clinical Message

Systemic lupus erythematosus should be included in the differential diagnosis of every adolescent with pancytopenia. An accurate diagnosis with the appropriate therapy is vital and can cause lasting reversal of this condition.

Keywords

Aplastic anemia, pancytopenia, systemic lupus erythematosus.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown etiology characterized by the presence of autoantibodies and immune complex deposition. Hematological manifestations are very common and are one of the classification criteria of the American College of Rheumatology (ACR) [1]. Thrombocytopenia occurs in 25–50% of the patients, leucopenia in approximately 50% and Coombs' positive hemolytic anemia in about 10% [2, 3]. The cytopenias can occur singly or in combination. They are usually the result of autoantibody-mediated peripheral destruction with associated hypercellular bone marrow. Although hematological manifestations are common, they are seldom the sole presenting feature of the disease [3]. Most often, cytopenias appear during the course of the disease, but occasionally aplastic anemia is the initial manifestation of SLE [4–7]. This may be underestimated due to the presumed peripheral destruction of the blood cells. In this paper, we describe 2 adolescents with aplastic anemia as the presenting feature of pediatric SLE.

Case Presentations

Case 1

A 16-year-old girl presented with oligomenorrhoea and recurrent epistaxis. Full functional inquiry was normal, but her parents had noticed photosensitivity of the face especially in the summer at a young age. Her past health was normal. She was born in Canada; her parents are of Asian descent and are non-consanguineous.

Physical examination revealed a malar rash, three café-au-lait spots, but was otherwise normal without lymphadenopathy, hepatosplenomegaly or arthritis.

Laboratory examination showed a platelet count of 23×10^9/L, white cell count of 3.9×10^9/L with absolute neutrophil count (ANC) 1.34×10^9/L, lymphocyte count 1.41×10^9/L, and hemoglobin 147 g/L with a normal reticulocyte count. The international normalized ratio (INR) was 1.0 and the partial thromboplastin time (PTT) was 26 sec. Urine analysis was normal as were liver and renal function tests and complement levels. The IgG and IgA were elevated at 17.1 g/L and 5.6 g/L, respectively,

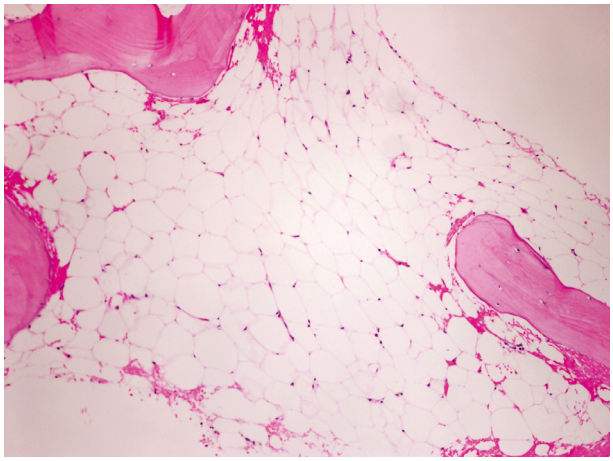

Figure 1. Bone marrow biopsy is revealing hypocellular marrow with a cellularity of far less than 20% (Case 1).

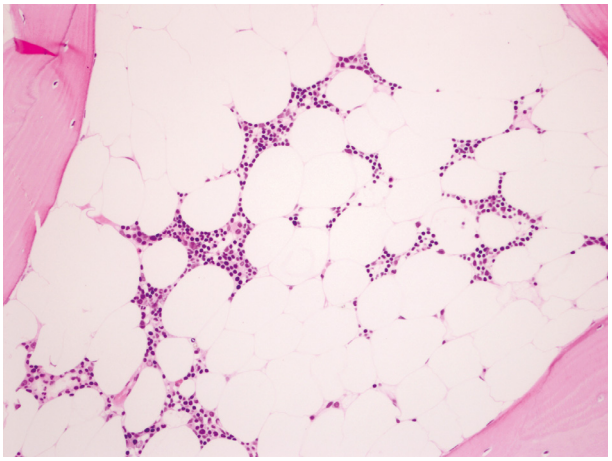

Figure 2. Bone marrow biopsy showed hypocellular marrow, consistent with aplastic anemia (Case 2).

with a normal IgM at 1.0 g/L. Antinuclear antibody (ANA) was positive at 1:160 but anti-double stranded DNA, rheumatoid factor, anti-SM, anti-RNP, anti-Ro, and anti-La antibodies were all negative. Anticardiolipin antibodies were equivocal by enzyme-linked immunosorbent assay, but lupus anticoagulant was negative. Spontaneous and induced (MMC (mitomycin C), DEB (diepoxybutane)) chromosomal breakage studies, to exclude Fanconi anemia, were not elevated.

Bone marrow aspiration and trephine biopsy (narrow, cylindrically shaped solid piece of bone marrow) revealed a hypocellular marrow with a cellularity of less than 20% (Fig. 1). The normal cellularity of the bone marrow at her age is around 60%. There were no signs of malignancy. Megakaryocytes were present but in reduced numbers. Erythropoiesis was active and mainly normoblastic. All stages of granulopoiesis were reduced. Stromal elements were easily seen.

She fulfilled the classification criteria for SLE (photosensitivity, a malar rash, hematologic criteria and immunologic criteria [positive ANA]) and a diagnosis of SLE was made [1]. Hydroxychloroquine 300 mg once daily was started, and her blood counts have gradually improved. Laboratory examination after 2 years showed a platelet count of 105×10^9/L, ANC 1.84×10^9/L, and hemoglobin 128 g/L.

Case 2

A 15-year old boy presented with bruising and petechiae. Functional inquiry revealed a history of resolved hepatitis of unknown etiology (all viral studies were negative and no toxins or reactions to medication were noted) 1 year previously. His family had emigrated from Afghanistan to Canada when he was an infant. His parents are non-consanguineous.

Physical examination revealed bruises and petechiae; the remainder was unremarkable without lymphadenopathy, hepatosplenomegaly or arthritis.

Laboratory examination showed a platelet count of 31×10^9/L (lowest 12×10^9/L), hemoglobin of 135 g/L, and white blood cell count of 3.5×10^9/L with an ANC of 1.31×10^9/L. He had a normal urinalysis with normal renal, liver function, serum immunoglobulins, and mildly elevated C-3 complement**.** Haptoglobin and LDH were normal. Platelet antibodies were positive. Bone marrow examination showed a hypocellular marrow, consistent with aplastic anemia (Fig. 2).

He was treated with a short course of prednisone and IVIG (Intravenous Imunoglobulin) under the suspicion of acute ITP (Idiopathic thrombocytopenic purpura), and a mild improvement on the platelet count was noticed, but he developed normocytic anemia with absolute reticulocyte count of 65×10^9/L and neutropenia. Over the ensuing months he complained of bilateral wrist pain with swelling and morning stiffness with no other new symptoms. The only change in laboratory blood work was a positive ANA at a titer of 1:40 and positive anti-Ro antibodies but negative anti-double stranded DNA, anti-SM, anti-RNP, anti-La antibodies, and rheumatoid factor. His anticardiolipin level was borderline elevated, but lupus anticoagulant was negative. His C-3 complement was still mildly elevated, while his C-4 complement level was normal. Physical examination was remarkable for a malar rash, some palatal petechiae, and polyarthritis. There was no hepatosplenomegaly or significant lymphadenopathy.

On the basis of a malar rash, arthritis, and the hematologic and immunologic criteria, he fulfilled the classification criteria for SLE and a diagnosis of SLE was made [1]. Prednisone at 20 mg once daily and hydroxychloroquine

Table 1. Children with lupus who presented with pancytopenia reported in the literature.

Author	Year	Age	Sex	Onset aplasia[1]	Treatment	Response	Reference
Brooks	1984	17 years	Female	7 months	Pp	Remission	[4]
Bailey	1989	17 years	Female	1 month	Pp/Steroids	Remission	[5]
Sumimoto	1991	6 years	Male	2 months	MP	Remission	[6]
Wolach	1993	5 months	Female	5 months	Pred	No response	[7]
Present report	2008	16 years	Female	0 month	Hchl	Remission	
Present report	2008	15 years	Male	−3 months	Pred/Hchl	Remission	

Pp, plasmapheresis; MP, methyl prednisolone; Pred, prednisone; Hchl, hydroxychloroquine.
[1]Onset aplasia related to the diagnosis of systemic lupus erythematosus.

400 mg once daily were started and after several weeks marked clinical improvement was noted. His follow-up blood counts revealed a normal hemoglobin and white blood cell count with an improvement in the platelet count to $>50 \times 10^9$/L.

Discussion

Aplastic anemia has been described in patients with SLE and is most commonly seen following the diagnosis of SLE while presentation before or at the time of diagnosis of SLE is unusual [8] and only a limited number of patients are reported in the pediatric medical literature (see Table 1). In a 2002 review, 17 patients with SLE and aplastic anemia (13 adults and 4 children), wherein the aplastic anemia preceded the diagnosis of SLE in only 18% of the cases (3 adults) [9]. Since that report, there has been one additional case of aplastic anemia reported at the time of diagnosis in a 22-year-old woman [4–6, 9, 10].

The only previously reported case of aplastic anemia around the time of diagnosis of pediatric SLE was in a 6-year old girl with a 3-year history of chronic ITP, presenting with fever, arthralgia, oral ulcers, pleuritis, alopecia, and a malar rash. Autoantibodies were found. Three months later she developed pancytopenia and a bone marrow aspirate was hypocellular [6].

Although cyclosporine and antithymocyte globulin are commonly used in idiopathic aplastic anemia; its use in aplastic anemia associated with SLE is very limited and as suggested by our patients, intensive immunotherapy may not be required for SLE patients. Our patients, with mild pancytopenia, responded to hydroxychloroquine and moderate doses of prednisone and hydroxychloroquine, respectively. This is in contrast to the previous reports in the literature which showed that the majority of cases required a second immunosuppressive agent in addition to oral corticosteroids or pulse methylprednisolone to obtain a response [4–6, 9, 10]. In children, plasmapheresis has been used in addition to corticosteroids, while in adults also cyclophosphamide, azathioprine, and oxymethalone have been used [10, 11].

The long-term outlook after the recovery from aplastic anemia with SLE is very good, especially in comparison with idiopathic acquired aplastic anemia.

In patients with SLE, the immune-mediated cytopenia is secondary to antibodies directed to one or more cell lines resulting in peripheral destruction. However, in our cases and in the previously reported cases of aplastic anemia secondary to bone marrow failure, studies have failed to demonstrate peripheral destruction and in most cases the etiology of the bone marrow failure was not defined. Different mechanisms of aplastic anemia have been considered in the literature. An IgG complement-dependent antibody [4] or a non-complement-dependent antibody suppressing early hematopoietic progenitor cells [5], but also an auto-immune cellular process inhibiting bone marrow progenitor cells [12] or a cytotoxic lymphocyte activation suppressing the hematopoiesis [7, 13] have been proposed. Two large studies examined bone marrows of SLE patients with cytopenias. One showed either global hypocellularity or granulocytic hypoplasia [14] while the other showed stromal bone marrow damage, bone marrow necrosis and dysplasia of all hematopoietic lineages. The latter study did not find a correlation of the severity of peripheral cytopenias with the cellularity and distribution of individual hematopoietic lineages [15].

Conclusion

Only limited number of cases of aplastic anemia associated with SLE are described in the literature. We suggest that this is likely the result of the presumption that the pancytopenia in SLE is always secondary to the peripheral destruction of the blood cells. We therefore suggest that SLE should be included in the differential diagnosis of a child with pancytopenia and the appropriate investigations for SLE should be undertaken. In addition, as demonstrated by our second case, patients should be serially followed for the subsequent development of SLE. Similar to what is seen in other SLE manifestations, both antibody-mediated and T lymphocyte-mediated mechanisms

may lead to the bone marrow failure in SLE patients. An accurate diagnosis with the appropriate therapy is vital and can cause lasting reversal of this condition.

Conflict of Interest

None declared.

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