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Original Article

Hemolytic anemia developed in Kimura's disease: a case report

Ying Li, Junru Liu, Chang Su, Juan Li

Department of Hematology, First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China

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Abstract: Kimura's disease (KD) is a rare chronic inflammatory disorder that involves the lymph nodes, skin, kidneys and ears, but its influence on the hematologic system remains unknown. We discovered a rare case of KD that developed hemolytic anemia. Erythrocytes hyperplasia with eosinophilia were observed in the bone marrow smears, while eosinophilic abscesses and endothelial proliferation could be found in the lymph node, which were strong proof for hemolytic anemia with KD. Flow cytometry analysis revealed diminished expression of CD55 and CD59 on the blood cell surfaces, which might explain the reason of hemolytic anemia. The symptoms of the patient could not be relieved by prednisolone but responded well to the treatment with cyclophosphamide. The abnormal clone of blood cells disappeared after cyclophosohamide. To the best of our knowledge, this is the first case of hemolytic anemia developed in a patient with KD and we discovered the possible pathogenesis of the disease.

Keywords: Kimura's disease, paroxysmal nocturanal hemoglobinuria, CD55, CD59, cyclophosphamide

Introduction

Kimura's disease (KD) is a rare inflammatory disorder that is endemic in Asia. It is characterized by painless cervical lymphadenopathy and subcutaneous masses, as well as eosinophilia in both blood and tissues with elevated serum IgE [1, 2]. Typical histologic characteristics of KD include clustering of eosinophils forming an eosinophilic abscess, vascular proliferation and hyperplastic endothelium [2]. Most cases of KD involve lymph nodes and salivary glands, and there are some case reports of KD identified in less frequent locations such as kidneys, ears, eyes, spermatic cords, and the median nerve [3]. But to our knowledge, the hematologic changes of KD remain unclear. Here we present a case of a KD patient who developed hemolytic anemia during clinical course and treatment.

Materials and methods

Subject

This study was approved by the Institutional Review Board. A 17-year-old girl was observed from her diagnosis at June, 2012 to June 2016. She was first admitted to our hospital complaining of pruritus with rashes for 6 months and fatigue for 1 month. Skin biopsy in the local clinic showed eosinophilia and she was diagnosed with atopic dermatitis. The patient was given a steroid ointment but it failed to relieve her symptoms. Physical examination on admission revealed multiple enlarged lymph nodes in the cervical, axillary and groin area with maximal diameters of up to 6 cm. The laboratory tests of peripheral blood showed that the patient's hemoglobulin was low at 68 g/L (reference range, 113-151 g/L); red blood cell count was reduced to 2.64×10^{12}/L (reference range, $3.68\text{-}5.13\times10^{12}$/L), while the percentage of reticulocytes was as high as 2.5% (reference range, 0.5-1.5%); eosinophil cell count was elevated to 1.51×10^{9}/L (reference range, $0.02\text{-}0.50\times10^{9}$/L). Urine latent blood test was positive and elevated indirect bilirubin of 21.1 μmol/L (reference range, 0-15 μmol/L) was found in the serum. ^{18}F-FDG PET/CT scan showed lymphopathy as well as bone changes with a maximal standardized uptake value (SUV) of 3.6 (**Figures 1A** and **2A**).

Bone marrow examinations

Clinical information was obtained from the patient's medical records. Bone marrow smears

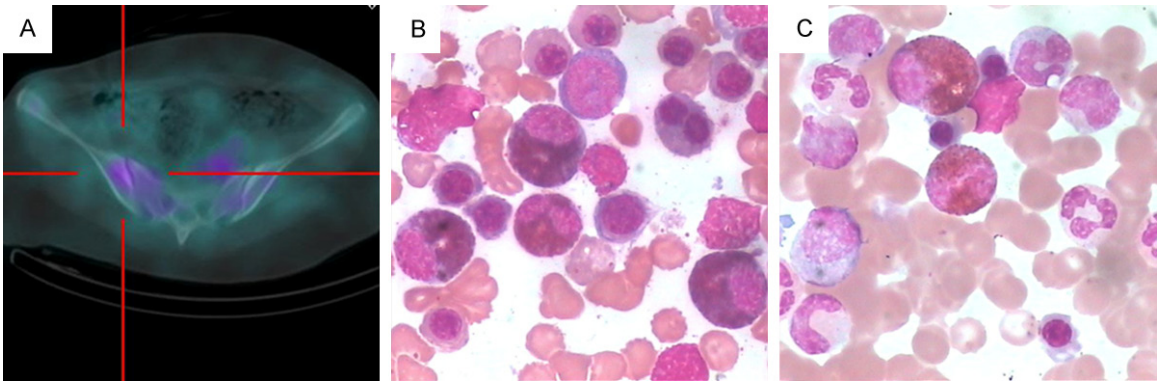

Figure 1. Ilium changes in PET/CT and bone marrow smears photomicrographs of ilium. A: Bone changes with elevated uptake of FDG in the ilium. B: Bone marrow smear at the time of diagnosis: basophilic, polychromatophilic and orthochromatic normoblast increased, indicating erythrocytes hyperplasia, while eosinophilic cells with brick-red small granules in the cellular cytoplasm were also observed (Giemsa and Wright staining, original magnification: ×1000). C: Bone marrow smear after cyclophosphamide: eosinophilia still existed without erythrocytes hyperplasia (Giemsa and Wright staining, original magnification: ×1000).

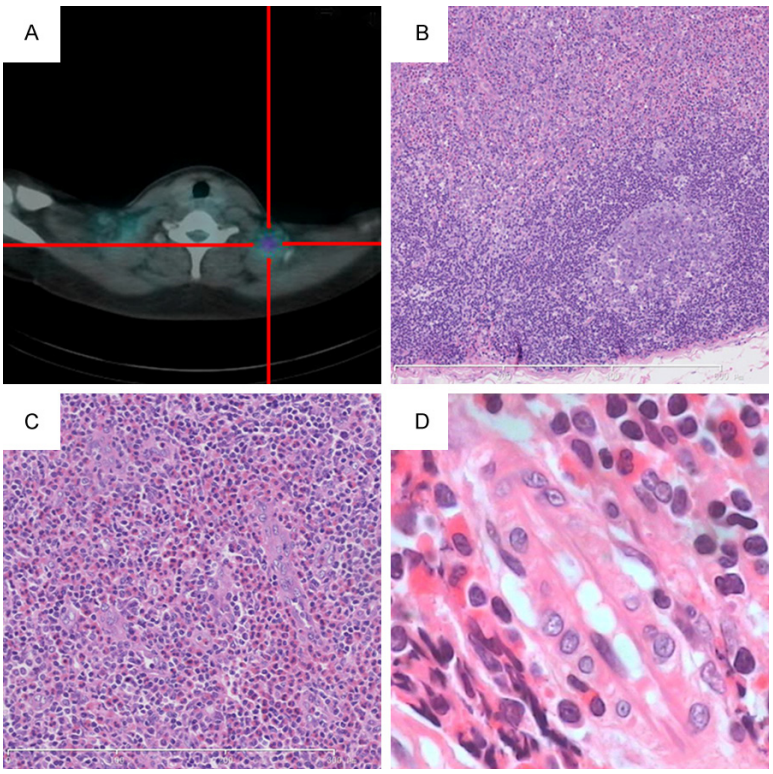

Figure 2. Lymphopathy of the left supraclavicular fossa in PET/CT and the pathology photomicrographs. A: Lymphopathy with elevated uptake of FDG in left supraclavicular fossa. B: Reactive lymphoid follicles with germinal centers, eosinophils and vessel proliferation were seen in the lymph node (Hematoxylin and Eosin staining, original magnification: ×100). C: Eosinophilic abscesses and endothelial proliferation could be found in the lymph node (Hematoxylin and Eosin staining, original magnification: ×200). D: The endothelial cells were flattened with eosinophilic abscesses in the lymph node (Hematoxylin and Eosin staining, original magnification: ×400).

of the ilium were routinely processed and were stained with Giemsa and Wright. Gross specimens of the lymph node and hematoxylin-eosin-stained slides were examined. Routinely processed, formalin-fixed, paraffin-embedded tissue sections were stained with hematoxylin and eosin. Fluorescent in situ hybridization (FISH) of platelet-derived growth factor receptor (PDGFR) α and PDGFR β were performed in the bone marrow cells according to standard protocols [4], using fluorescein-labelled probes for PDGFR α and PDGFR β (Abbott Molecular, USA). Flow cytometry analysis of CD55 and CD 59 of the peripheral blood was carried out in BD FASCanto system, using CD55 and CD59 antibodies (BD Biosciences, USA).

Results

Microscopic findings of cytology

Basophilic, polychromatophilic and orthochromatic normoblast increased in the bone marrow smear, indicating erythrocytes hyperplasia, while elevated percentage of eosinophilic cells with brick-red small granules in the cellular cyto-

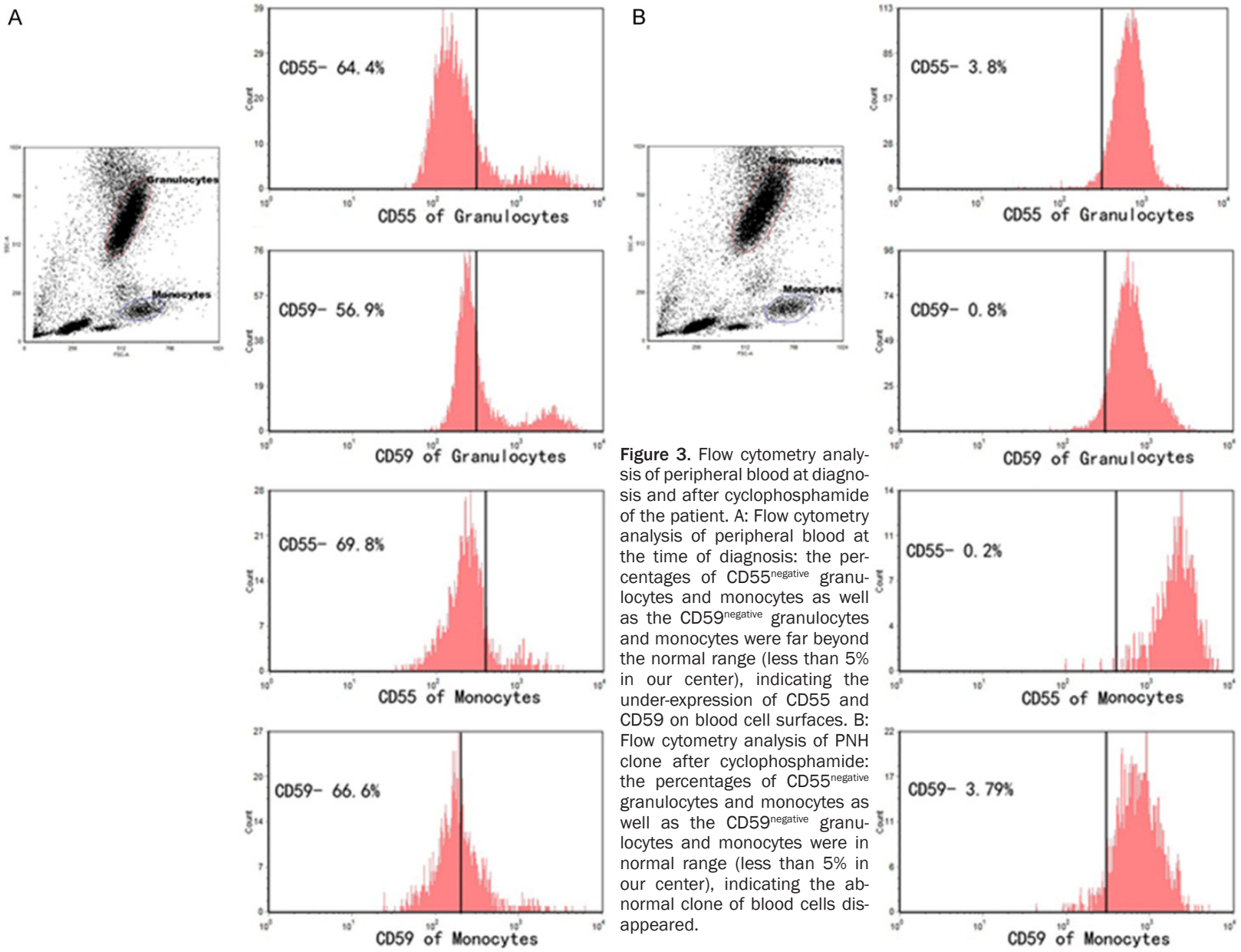

Figure 3. Flow cytometry analysis of peripheral blood at diagnosis and after cyclophosphamide of the patient. A: Flow cytometry analysis of peripheral blood at the time of diagnosis: the percentages of $CD55^{negative}$ granulocytes and monocytes as well as the $CD59^{negative}$ granulocytes and monocytes were far beyond the normal range (less than 5% in our center), indicating the under-expression of CD55 and CD59 on blood cell surfaces. B: Flow cytometry analysis of PNH clone after cyclophosphamide: the percentages of $CD55^{negative}$ granulocytes and monocytes as well as the $CD59^{negative}$ granulocytes and monocytes were in normal range (less than 5% in our center), indicating the abnormal clone of blood cells disappeared.

plasm was also observed. Pathologic examination of the lymph nodes in the supraclavicular fossa revealed eosinophilic abscesses in reactive lymphoid follicles with germinal centers and vascular proliferation; flattened vascular endothelial cells were also found (**Figure 2B-D**). These typical histopathologic features supported a diagnosis of KD [2].

Immunology and molecular biology findings

Flow cytometry of the peripheral blood revealed diminished expression of CD55 and CD59 on the surfaces of both granulocytes and monocytes, which indicated the increased susceptibility of the blood cell membrane to the lytic activity of complement (**Figure 3A**).

FISH of PDGFR α and PDGFR β mutation was negative in the bone marrow cells, which helped to exclude the diagnosis of hypereosinophilic syndrome.

Follow-up

The patient was started on prednisolone 50 mg per day for 1 month. However, her symptoms of fatigue, pruritus and enlarged lymph nodes did not relieve and her hemoglobulin remained low at 82 g/L. She even developed multiple vein thromboses in her lower extremities during the treatment. Therefore, 3 cycles of intravenous cyclophosphamide 500 mg per 28 days were given and her symptoms were significantly relived. After the treatment, her largest lymph nodes shrunk to a diameter of 1.5 cm. Her hemoglobulin increased to 121 g/L and red blood cell count was 4.12×10^{12}/L. Bone marrow smears still showed eosinophilia but without erythrocytes hyperplasia (**Figure 1C**), while flow cytometry revealed normal expression of CD55 and CD59 on the surfaces of blood cells (**Figure 3B**). During the one year follow up after the end of treatment with cyclophosphamide, the patient was doing well with normal hemoglobulin and no enlargement of lymph nodes, although she still felt occasional pruritus.

Discussion

KD is a rare type of benign chronic inflammatory disorder, primarily involving young men in Asia [5]. The etiology of KD remains unknown, but most scholars believe it is caused by chronic infections, allergies, or tumors [2]. The most common presentations of KD are soft tissue swelling, cervical lymph node and salivary glands enlargements, and 98% of KD patients develop eosinophilia and elevated serum IgE [3, 6]. However, to our knowledge, no case of hemolytic anemia in KD patients had been reported thus far.

CD55 and CD59 are glycolsylphosphatidylinositol-anchored cell surface proteins, which inhibit the C3 convertases formation and prevent the polymerization of the membrane attack complexes to the cells. The diminished expressions of CD55 and CD59 on blood cell surfaces are most commonly found in patients with paroxysmal nocturnal hemoglobinuria, which is an acquired clonal disorder of hematopoietic stem cells [7]. However, in some patients with autoimmune disorders such as autoimmune hemolytic anemia and systemic lupus erythematosus, CD55 and CD59 deficiency can be also detected in peripheral blood [8]. Scholars believe that autoantibodies on cells of hematopoietic lineage may be responsible for the under expression of CD55 and CD59, and CD55 and CD59 play a facilitatory role rather than a triggering role in hemolytic anemia [9].

KD is also a type of inflammatory disorder and results in autoantibodies [10]; therefore, it may explain the diminished expression of CD55 and CD59 on blood cells surfaces and hemolytic anemia as well. Our hypothesis is also supported by the fact the patient responded to cyclophosphamide rather than prednisolone, the latter of which is the first line medication for paroxysmal nocturnal hemoglobinuria and should have resolved the hemolytic anemia.

Due to its rarity and complexity, there are diagnostic challenges to explain the coexistence of lymphopathy, eosinophilia, and hemolytic anemia. To our knowledge, this is the first case describing hemolytic anemia in a patient with KD. The observations of the present case may help to establish a better understanding of hematologic changes of KD.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Juan Li, Department of Hematology, First Affiliated Hospital of Sun Yat-sen University, Guangzhou 510080, Guang-

dong, China. Tel: +86-20-13719209240; Fax: +86-20-87333455; E-mail: 13719209240@163.com

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