Pancytopenia and severe sepsis in an adult case of congenital X-linked agammaglobulinemia (XLA)

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LETTER TO THE EDITOR

Pancytopenia and severe sepsis in an adult case of congenital X-linked agammaglobulinemia (XLA)

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Dear Editor,

Pancytopenia is a common cause of patient's admission in a hematology ward, usually due to neutropenia-related infections, like pneumonia. Other than usually recorded pathogenetic mechanisms, such as bone marrow (BM) failure due to infiltrative malignant diseases or by the several causes of BM aplasia, pancytopenia may be due to rare causes, which should be carefully taken into account in order to avoid mistaken diagnosis and to establish a correct treatment approach, as demonstrated by the case recently observed and thereby reported by us.

A 34-years-old man was admitted in the emergency room of our hospital because of acute abdomen, which occurred after some days of antibiotic-resistant fever accompanied by a hemorrhagic and inflammatory lesion involving the skin of the left foot. At admission, he was pale and suffering; the physical examination revealed a diffuse abdominal resistance. The past personal and familial medical histories were not contributory. The initial ultrasound showed a gallbladder with an ultrasonographic Murphy sign, a significant wall thickening over 5 mm and pericholecystic fluid. The patient underwent abdominal computed tomography (CT) scans, which confirmed positive findings for acute acalculous cholecystitis only. A comprehensive laboratory evaluation revealed severe pancytopenia with leucopenia (white blood cells=0.23×10^3/mcL with 0.020×10^3/mcL neutrophil), mild anemia (hemoglobin=10.9 g/dL), and thrombocytopenia (platelet count=88×10^3/mcL). A BM aspirates was then performed; the evaluation of BM smears revealed a normal BM cellularity with absence of megakaryocytic features and an increase in the number of mitotic erythroid (30%) and granulocytic (70%) cells; a maturative arrest of granulocytopoiesis with excess of promyelocytic (90% of granuloblasts), without blasts or hemophagocytosis, was observed (Fig. 1). No lymphocytes were detected. A provisional diagnosis of acute myeloid leukemia was made. Soon after, the patient developed a sudden respiratory failure and a severe shock with renal impairment, requiring admission in intensive care unit where he received hemodynamic and respiratory support, while an antimicrobic therapy with meropenem and amikacin was started. A chest CT scan revealed lung infiltrates suggesting a bilateral pneumonia, associated with multiple bronchiectasia. Blood cultures were negatives. Bronchoalveolar lavage was not performed due to patient's poor clinical conditions. The patient's clinical conditions slowly improved. A CT scan performed 1 week after the start of the antibiotic therapy revealed only a mild reduction of lung infiltrates; cutaneous lesion of foot

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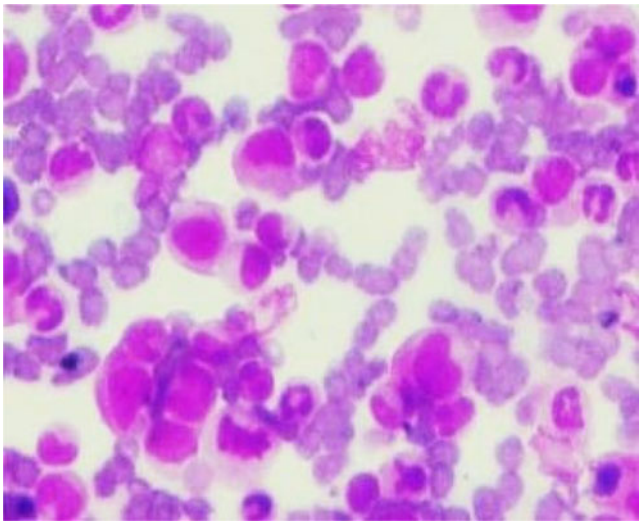

Fig. 1 Bone marrow smear, ×1,000; maturative arrest of granulocytopoiesis with excess of promyelocytic forms

was stable without any improvement; thus far, amikacin was replaced for teicoplanin with partial response. Although cultural studies did not reveal the etiology of infection, response to teicoplanin suggested that a Gram-positive bacteria were like involved. Laboratory findings showed a progressive normalization of blood cell count with resolution of lymphopenia; a BM aspirate 1 week after the admission showed normally maturating hemopoiesis; however, lymphocytes were still absent, so that immunoglobulin (Ig) blood concentrations were evaluated and a lymphocyte subset analysis was performed. Ig levels were remarkably reduced (IgG=4.8 (range=6.9-16); IgA=0.41 (range=0.7-3.78) and IgM=0.39 g/L (range=0.6-2.63)); moreover, a near absence of B lymphocytes (CD19+ <2%) and a reduction of CD4+ lymphocytes (0.0681×10^3/mcL) with a CD4/CD8 ratio (0.65) inversion were detected. Human immunodeficiency virus and hepatitis serology, as well as Epstein-Barr virus-polymerase chain reaction were negative. Intravenous immunoglobulins (IVIG) administration was started. A chest CT scan was then repeated 2 weeks after admission, revealing a significant improvement of pneumonia. In the view of these laboratory and clinical findings, an underlying cause of the immunodeficiency was carefully searched for by a molecular analysis of peripheral blood. A definitive diagnosis of X-linked agammaglobulinemia (XLA) was made based on the detection of a new missense substitution in exon 15 (c. 1,487 T>G, seq. X58957) causing a leucine change to arginine (in position 452 of the TH protein domain in the Bruton's Tyrosine kinase (Btk) gene) resulting in protein absence (Western blot; Fig. 2). This alteration, not reported in literature yet, was excluded in 100 healthy donors. The patient, presenting good general conditions and having achieved the full recovery from the pneumonia and the cutaneous lesion, was discharged on day 22 with the program of monthly IVIG infusions. To date, 10 months after the admission, is well and active. Laboratory findings are still normal.

X-Linked or Bruton's Agammaglobulinemia is a congenital X-linked inherited disorder caused by mutations in the gene coding for the Btk which is implied in the development of B cells. Mutations of Btk gene cause the incomplete differentiation of B cells precursors to mature B cells or the inefficient expansion of pre-B cells into later B cells stages. [1]. XLA is characterized by a defect in the peripheral blood B cells (CD19+<2%) and very low levels of immunoglobulins, resulting in increased susceptibility to bacterial infections (sinusitis, pneumonia, pyogenic dermatitis, and osteomyelitis). Patients usually become symptomatic in infancy or early childhood after their maternal immunoglobulins have been lost [2]. Adult presentation of XLA is very unusual [3]. Neutropenia is a well described features of XLA, occurring in about 11-18% [4, 5] of patients at diagnosis and up to 25% [6, 7] during the entire disease course and being mainly due to viral infections or immune-mediated effects; adequate Ig replacement therapy leads to a remarkable reduction of its occurrence [5]. The observation of BTK expression both in lymphoid and myeloid lineage BM cells, may suggest the hypothesis of a direct role on the occurrence of neutropenia exerted by the BTK genetic deficiency [8]. Aplasia seems to be a rare event in the course of XLA although causal mechanisms of neutropenia could involve granuloblasic series alone as well as the full hemopoiesis. In conclusion, at the best of our knowledge, we have reported the first case of trilinear cytopenia in a XLA patient, our experience suggesting that humoral immunodeficiencies and B cell defects, although rarely diagnosed first in adulthood, should be taken into account in the evaluation of a pancytopenic patient with fever in order to avoid diagnostic mistakes and to plan a rationale and appropriate treatment approach.

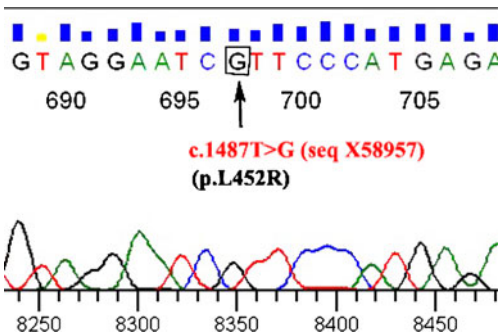

Fig. 2 Btk gene molecular analysis, performed by denaturing high performance liquid chromatography and sequencing, revealed a new missense substitution in exon 15 (c.1487 T>G, seq. X58957) leading to a change from the normal leucine at the site to an arginine in the TK protein domain

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