

Autoimmune Transient Neutropenia: A Case Report

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Summary

Autoimmune transient neutropenia is a rare disorder characterized by neutropenia in early life, usually before 2 years of age. The disease is manifested mainly through skin and upper respiratory tract infections. We report the case of a seven-month old patient with autoimmune transient neutropenia and describe her clinical progression.

Keywords: Autoimmune transient neutropenia; Vulvar ulcer; Congenital agranulocytosis; Pediatric

Introduction

Autoimmune transient neutropenia is a rare condition characterized by neutropenia associated with recurring infections in early life. In childhood, neutropenia can be a manifestation of several illnesses and has important clinical repercussions for the patients. This article is aimed at reporting one such case.

Clinical Case

A female Caucasian patient aged seven months and seven days presented with a painful volume in the clitoral region associated to persistent diarrhea for over two weeks, without systemic symptoms. Topical antibiotic and warm compresses were used with full lesion regression.

The patient presented with two more episodes of small vulvar abscesses in the following two months, which improved with the previous treatment (self-medication). At age nine months, there was recurrence of the abscess and vulvar ulcerations (**Figures 1-3**). The patient did not respond to local and oral antibiotic treatment. She presented with concomitant respiratory infection, in addition to diarrhea, high fever, intense local pain and overall health impairment.

Prior history: the umbilical stump fell off 41 days after birth. The patient did not present any infectious manifestations until the sixth month of life, when she started attending a crèche. She presented with repetition respiratory infections and frequent diarrhea since then.

On examination, she presented with pale skin and mucosa, irritability at being handled, 38.5°C fever, increased volume in the clitoral region, with erythema, warmth and local pain, pustules and small ulcerations with areas of central necrosis in the small labia.

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The blood count showed discrete anisocytosis, microcytosis and hypochromia. Found values: RBC 4.2 M/uL; Hemoglobin 9.2 g/dL; Hematocrit 29.6%; MCV 22.1 fL; MCHC 31.1 g/dL; RDW: 17.8%; Leukocytes: 10.520/uL; Metamyelocytes 3%; Rod cells 5%; Segmented 0%; Eosinophils 3%, Basophils ***%; Lymphocytes 75%; Monocytes 10%; Platelets 408,000/uL.

The secretion culture showed *Pseudomonas aeruginosa*. The follow-up CBC showed agranulocytosis, discrete anisocytosis and moderate thrombocytosis. Found values: RBC 4.3 M/ μ L; Hemoglobin 9.5 g/dL; Hematocrit 30.3%; MCV 70.8 fL; MCHC 31.4 g/dL; RDW: 17.8%; Leukocytes: 9,420/ μ L; Metamyelocytes 0%; Rod cells 0%; Segmented 0%; Eosinophils 3%, Basophils 0%; Lymphocytes 91%; Monocytes 6%; Platelets 815,000/ μ L.

The myelogram showed hypocellular bone marrow for her age, with a dilutional component; rare and normocellular lumps. All the series were present, well represented and without significant morphological abnormalities. The smear analysis showed two histiocyte phagocytizing neutrophils and one histiocyte phagocytizing a macroplatelet.



Figure 1 Ulcerated and necrotic lesion in the clitoral region.



Figure 2 Ulcerated lesion in the vaginal introitus and large labia.



Figure 3 Abscess with purulent secretion drainage.

Discussion

Neutropenia is defined as the presence of abnormally few neutrophils in the blood (less than 2000 neutrophils/mm³ blood in children aged 2 to 12 months and less than 1500 neutrophils/mm³ blood in children older than one year). It can be classified in different levels: mild (1,000-1,500 neutrophils/mm³ blood), moderate (500-1,000 neutrophils/mm³ blood) or severe (less than 500 neutrophils/mm³ blood). It is considered chronic when the neutrophil count has remained low for the last three months [1].

Neutropenia is also analyzed when there is cell depletion of bone marrow. Central neutropenia occurs when there is low neutrophil

count in bone marrow, which evidences deficiency in the early stages of maturation; peripheral neutropenia occurs when neutrophil maturation in bone marrow is normal [1].

The most common cause of acquired neutropenia is viral infection, followed by drugs and autoimmune neutropenia. Congenital neutropenia is usually diagnosed by invasive acute bacterial or fungal infections, which are life-threatening [2].

Congenital neutropenia is characterized by a constitutional defect in a specific gene. The most common cause for severe neutropenia is mutations in the ELA2 or ELANE gene, of autosomal dominant inheritance [3]. However, Kostmann Syndrome is commonly considered a paradigm of congenital neutropenia [4]. This syndrome is also a severe form of neutropenia and consists of recessive autosomal mutations in the HAX1 gene [1]. Other genetic mutations have already been identified and related to congenital neutropenia, but they are responsible for a smaller percentage of cases [3].

Neutropenia is found with relative frequency, but congenital neutropenia is quite rare [4]. Since neutropenia of infancy can be a symptom of various syndromes, it requires careful monitoring. It is usually not the main complaint, but can lead to the development of severe infections that require some precautions [3].

The sites preferentially affected by infection are highly variable. The most frequent are the following: the skin, the mucosae and the gastrointestinal, respiratory and genitourinary tracts. Oral disorders manifest frequently patients with central and severe chronic neutropenia, as erosive and hemorrhagic stomatitis, gingivitis, and ulcers in the tongue. Diffuse gastrointestinal lesions can be present, causing abdominal pain and diarrhea associated to perianal infection and ulceration. Infection symptoms can be atypical in patients with severe deep neutropenia who will develop local inflammation with necrotic tendency. Bacterial colonization is more common and generally involves *Staphylococcus aureus*, *S. epidermidis*, *Streptococcus spp.*, *Enterococcus spp.*, *Burkholderia cepacia*, *Nocardia asteroides*, *Pneumococcus spp.*, *Pseudomonas aeruginosa* and gram-negative bacilli. Some fungal infections involve *Candida albicans* and *Aspergillus spp.* [3,4].

Persistent Neutropenia requires investigation as it entails infectious complications. Nowadays, cytogenetic studies on bone marrow are considered crucial for isolated neutropenia investigation, especially when it is suspected to be congenital [4]: the major determinant in the relationship between neutropenia and infection is the neutrophil count in bone marrow [2].

Satisfactory results have been obtained with the introduction of granulocyte colony stimulating factor (G-CSF) to treat patients with chronic neutropenia. Patients who use this drug have normalized neutrophil count, reduced recurrent infections and inflammatory symptoms reduced by over 90%. Good responses for congenital neutropenia are obtained with high doses of G-CSF [2].

A bone marrow transplant is indicated for cases that are severe and refractory to drug treatment [1,4]. Transplant is the only curative option for patients with severe congenital neutropenia. Ideally, these patients should be identified as early as possible and the transplant should use the best available donor [5].

Acquired neutropenias are caused by a shortening of the neutrophil lifetime due to their destruction or increased consumption in peripheral blood. Primary autoimmune neutropenia is classified as an acquired neutropenia and is a rare disease. It is more commonly observed in girls and children younger than two years old [2]. In most cases, the course of the disease is benign and self-limited [6].

Autoimmune neutropenia frequently manifests through skin and upper respiratory tract infections. The gold standard for diagnosis consists of the presence of neutrophil-specific autoantibodies. In these patients, the bone marrow has no abnormalities. In general, the disease has good prognosis and neutropenia improves spontaneously. Although the total neutrophil count varied from 0 to 150/mm³, infections are mild [2].

Severe complicated infections are usually less frequent in children with autoimmune neutropenia than with genetic neutropenia. Many authors suggest prophylactic antibiotic (Trimethoprim/sulfamethoxazole) to reduce infection frequency in patients with autoimmune disease. It is also suggested that G-CSF be started in case of serious infections [6].

Behçet's disease, a neutrophilic dermatosis characterized by recurring oral and genital ulcerations and systemic manifestations, should be discarded as a differential diagnosis of vulvar ulcer. Pustular lesions in the oral mucosa tend to be small, with well-defined margins and an erythematous halo, similar to recurring thrush. The genital ulcers are similar and sometimes lead to scarring [7].

It is of utmost importance to dismiss sexually transmitted diseases, both congenital and acquired (sexual abuse). Infection by the herpes simplex virus has been observed and can manifest through genital ulcerations. Co-infection by HIV usually leads to

the worsening of pre-existing lesions and the onset of unspecific symptoms such as fever, myalgia, vomiting, diarrhea and abdominal pain [8].

Another differential diagnosis for genital lesions is ecthyma gangrenosum, a classic manifestation of invasive infection, usually caused by *Pseudomonas aeruginosa*. It manifests through gangrenous ulcers with grayish-black eschars involved by an erythematous halo. The lesions usually appear in immunocompromised patients and are distributed especially in the perineal or gluteal region, extremities, trunk and face [9].

Fournier gangrene presents lesions similar to those manifested by this patient. It is also called infections necrotizing fasciitis and involves the perineal region and external genitalia. It rarely affects children, but when reported in children, it is commonly associated with omphalitis, strangulated hernia, prematurity, rashes, chickenpox, circumcision and perineal abscesses. The main etiological agents for children are Streptococcus, Staphylococcus and anaerobes [10].

Regarding the patient reported here, the possibility of congenital neutropenia was assessed but the genetic testing was negative. A new bone marrow biopsy was performed which showed normocellular results, with normal cytogenetics and no dysplastic abnormality.

Thus, the diagnosis of autoimmune transient neutropenia was confirmed and treatment with granulocyte colony stimulating factor was started. The patient responded well to this drug, and the dose was gradually reduced until it was completely suspended and the patient maintained a good neutrophil level.

The patient was discharged from the outpatient Bone Marrow Transplant clinic since there was no indication for a transplant. She is under follow-up with a hematologist in her city of origin.

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