Agranulocytosis in a patient with acute Parvovirus B19 infection: a case study

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ABSTRACT

The definition of neutropenia is the reduction in the absolute number of neutrophils below 1.5×10^9. The chapter about acquired neutropenias affecting the adult population is of particular interest to the internist. PC, 75 years old man, was hospitalized because of fever, asthenia. In anamnesis: recent diagnosis of ulcerative pancolitis treated with mesalazine and corticosteroid therapy. During the hospitalization, to the fever resolution, we witnessed to a gradual reduction in the value of neutrophils leucocytes until the complete agranulocytosis. We set a therapy with granulocytes colony stimulating factors, and antifungal. The osteo-medullar biopsy confirmed a pure aplasia of the granulocyte marrow series without any evidence of cancer. The subsequent clinical development was favorable, with stable apyrexia and recovery of leucocytes count. Few days after, we received the positive response on the research of anti-Parvovirus B19 immunoglobulin M and in qualitative polymerase chain reaction. The patient was discharged with diagnosis *agranulocytosis in patient with acute infection of Parvovirus B19*. Neutropenia associated with Parvovirus infection is not frequent and is related to the presence of hematological diseases or condition of immunosuppression. The peculiarity of the case described is the complete agranulocytosis found: in fact in literature, only rare cases are described. Patient gave his informed consent.

Case Report

PC, 75 years old man, was hospitalized because of fever, asthenia and psychomotor braking.

In anamnesis: recent diagnosis of ulcerative pancolitis treated with mesalazine and corticosteroid therapy, ischemic heart disease (already subjected to percutaneous transluminal coronary angioplasty + bare metal stent), arterial hypertension, arterial disease of the lower limbs surgically treated, chronic vascular encephalopathy, hepatitis C virus (HCV) related hepatitis, benign prostatic hypertrophy, cholelithiasis, bearer of pacemaker.

At clinical examination, no pathological elements of relief emerged. The biohumoral exams showed a reduction in leucocytes and platelets (white blood cells: 2000; platelets: 85,000), increase in C-reactive protein (5 mg/dL). The chest X-rays resulted negative.

The ordinary microbiological examinations (blood cultures, urine cultures) were negative, as well as the controls of procalcitonin. The abdomen ultrasound showed only an increase in spleen dimension (14 cm) as in the past.

A broad-spectrum antibiotic therapy with ampicillin sulbactam was set.

During the hospitalization, to the fever resolution, we witnessed to a gradual reduction in the value of neutrophils leucocytes until the complete agranulocytosis.

An osteo-medullar biopsy was performed and, because of a drug-induced myelosuppression suspect, we stopped mesalazine, drug that was used over the last 2 months. Additionally, we set a therapy with granulocytes colony stimulating factors, and antifungal. The osteo-medullar biopsy confirmed a pure aplasia of the granulocyte marrow series without any evidence of cancer.

The subsequent clinical development was favorable, with stable apyrexia and recovery of leucocytes count. No bacterial or fungal infection occurred.

Among the requested verifications to investigate the possible cause of the agranulocytosis, we received few days after the positive response on the research of

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anti-Parvovirus B19 immunoglobulin M (IgM) and in qualitative polymerase chain reaction.

The patient was discharged on day 15 with diagnosis *agranulocytosis in patient with acute infection of Parvovirus B19*.

Differential diagnosis of neutropenia

The definition of neutropenia is the reduction in the absolute number of neutrophils below 1.5×10^9.

The causes of neutropenia are various and can be distinguished among: i) production defect; ii) increased destruction; iii) reduced survival.

The cause of neutropenia has to be recognized and treated because this condition increases the risk of infections, especially the bacterial and mycotic ones that prove to be greater in the presence of a greater number of neutrophils approaches 0.

The risk of infections is closely related to the causes, the degree and duration of neutropenia: it is low in otherwise healthy patient, and increases instead in patients that are already debilitated, malnourished, immunosuppressed, elderly, when reserves are already reduced.[1]

A separate chapter includes the congenital neutropenia, that are hereditary blood diseases usually identified during the childhood and adolescence, typically of pediatric interest.

In this area the Chediak Higashi disease, the cyclic family neutropenia, the severe family neutropenia, the Kostmann childhood agranulocytosis and the reticular dysgenesis can be included.[2]

The chapter about acquired neutropenias affecting the adult population is of particular interest to the internist.

The acquired neutropenias are divided into mild (neutrophils between 1 and 1.5×10^3), moderate (neutrophils between 0.5×10^3) and severe (neutrophils $<0.5\times10^3$).

A very frequent cause of neutropenia is associated with drugs. The pathogenetic mechanism may be a direct inhibition or antibody mediated. The incidence of neutropenia drug is estimated at 1-3 cases/one million people/year but the figure could be underestimated. Generally female patients and older age are affected. The drugs that give neutropenia (until agranulocytosis) are as follows: i) antibiotics: penicillins such as ampicillin and amoxicillin, cephalosporins, vancomicina, trimethoprim - sulfamethoxazole); ii) non-steroidal anti-inflammatory drugs: diclofenac, ibuprofen, sulfasalazine; iii) metimazolo, propylthiouracil; iv) antipsychotics: clozapine, phenothiazines, tricyclic antidepressants; v) antiepileptics: carbamazepine, phenytoin, valproate, ethosuximide; vi) cardiovascular drugs: flecainide, angiotensin-converting enzyme inhibitors, ticlopidine, digoxin; vii) diuretics: thiazides, furosemide, spironolactone; viii) chemotherapy drugs.[3,4]

Neutropenia can be observed in cancer patients with bone marrow involvement as in leukemias, lymphomas, multiple myeloma or metastatic solid tumors such as breast cancer or prostate.

The infections, that typically cause neutropenia (until the agranulocytosis), are usually viral as Epstein-Barr virus, citomegalovirus, varicella, measles, rubella, Parvivirus B19, influenza, hepatitis A, B, C, HIV. Neutropenia typically occurs during the first days of illness and persists for 7-10 days. The pathogenic mechanisms may relate to the production, survival, and distribution of neutrophils. Viruses can also induce the formation of antibodies causing a chronic immune neutropenia.

Even some bacterial infections can cause neutropenia such as those from *Staphylococcus aureus*, brucellosis, rickettsial, tuberculosis.

Patients with severe malnutrition can be leukopenic, in particular patients with a vitamin B12 deficiency and folic acid may have a granulopenia associated with classical macrocytic anemia. The neutropenia derives in this case from an ineffective erythropoiesis.

The autoimmune neutropenia may be idiopathic or secondary to autoimmune notes (systemic lupus erythematosus, rheumatoid arthritis, vasculitis), linked to drugs or infections. Specific antibodies IgG or IgM antineutrophil are well documentable with different methods; however the absence of antibodies does not exclude the diagnosis of autoimmune neutropenia, because antibodies against myeloid precursors may be present and not towards the mature neutrophils.

The neutropenia that is associated with hypersplenism (liver cirrhosis, leukemia) is generally associated with anemia and thrombocytopenia.[5,6]

Parvovirus B19 infection and agranulocytosis

The Parvovirus B19 is part of the Parvoviridae family. It is a virus that is strictly specific for the human series with a tropism for selective nucleated cells of the erythroid series. The virus was discovered in 1974, the infection is mainly transmitted by air and is commonly contracted during the infancy. 70% of the adult population has antibodies to the virus, indicating a previous infection. Usually the infection in immunocompetent patients is asymptomatic. A flu-like syndrome with fever and muscular pain may appear in the initial phase of the disease. After a few days a typical defined appearance skin called erythema infectiosum may occur at the level of the knees, especially in children ahead of a maculopapular rash on the rest of the body. In adults articular symptoms as arthralgia, rare cases of vasculitis, myocarditis, encephalitis and meningitis have been described. In patients who have an accelerated destruction of red blood cells (hemolytic anemia, iron deficiency, myelodysplasia), the Parvovirus infection may result in aplastic anemia. The virus is able to penetrate the

proerythroblast, induce apoptosis of progenitors, and lock in a transitory production of erythrocyte. Despite a tropism for proerythroblast, Parvovirus can cause other alterations of blood count as neutropenia, lymphopenia and a piastrinopenia.[7]

Generally neutropenia associated with Parvovirus infection is related to the presence of hematological diseases or condition of immunosuppression, although the underlying pathogenetic mechanism is not known in the literature and the described cases are very few.[8]

Discussion

Differential diagnosis is often a challenge for the Internist; the clinical case described above allows to dwell on the differential diagnosis of neutropenia. At first it was considered a drug-induced agranulocytosis considering mesalazine as the drug most recently introduced and described in the literature as a possible charge of agranulocytosis. The made osteo-medullar biopsy allowed to exclude the below lymphoproliferative disorders.

The patient with acute infection Parvovirus presented agranulocytosis, probably favored by an underlying condition of immunosuppression represented by the following factors: i) corticosteroid therapy that the patient had been performing for two months as a treatment of ulcerative pancolitis; ii) chronic liver disease HCV; iii) age advanced.

The clinical course was favorable: despite the presence of some risk factors mentioned above, the patient did not present infections related to agranulocytosis.

Conclusions

The peculiarity of the case described is the complete agranulocytosis linked to Parvovirus B19 acute infection: in fact in literature, only rare cases are described. In addition to the virus action, also mesalazine may have contributed to an absolute agranulocytosis.

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