Polymyalgia rheumatica, giant cell arteritis and myelodysplastic syndrome

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Abstract

The authors report a case of a 76-year-old male patient, with a previous diagnosis of polymyalgia rheumatica, admitted because of fever. After investigation, a giant cells arteritis and a myelodysplastic syndrome (refractory anemia with excess blasts), were diagnosed.

This association has been recently described by some authors. The physiopathology of these conditions suggest there is a significant rather than a chance association.

Keywords: polymyalgia rheumatica, giant cell arteritis, myelodysplastic syndromes, immunology.

Introduction

Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are syndromes most often diagnosed in patients over fifty years of age. It is common to find these two entities together, and many authors refer to polymyalgia rheumatica as a manifestation of giant cell arteritis, therefore, the two are a single entity. Although the etiopathogenesis is unknown, immunological mechanisms are involved.

Myelodysplastic syndromes (MDS) are entities associated with alterations in hematopoietic stem cells that lead to the appearance of inefficient hematopoiesis, with peripheral cytopenias with various clinical expressions and a high probability of transformation into acute non-lymphocytic leukemia. These syndromes are also more frequently diagnosed at advanced ages, and involve changes in humoral and cellular immunity, such as altered lymphocytes and monocytes that release lymphokines which can cause alterations in various target organs, in particular the vascular endothelium. This could be one of the physiopathological mechanisms responsible for the frequently described association of these syndromes with immunological and rheumatologic disease.[1,2]

The authors describe here the case of a patient, seventy-six years of age, with a previous diagnosis of PMR, who was hospitalized for febrile syndrome. Having ruled out infectious causes, a hypothesis of an association with GCA was proposed, based on an elevated sedimentation rate and symptoms of reduced visual acuity due to arteritis of the central retinal artery, supported by the response to treatment with corticosteroids. Concomitantly, non-iatrogenic pancytopenia was diagnosed, further study of which showed that it was MDS (refractory anemia with excess blasts – RAEB).

Case report

Male patient, seventy-six years of age, born and living in Sertã, retired. Diagnosed with PMR three years ago, treated with low doses of methylprednisolone (8 mg every other day), and asymptomatic until eight days prior to admission. At this time, he began to have fever, accompanied by vomiting of food, two episodes of diarrhea, complaints of pollakiuria, and one episode of lipothymia. He went his doctor, who prescribed ciprofloxacin, and his symptoms improved. On the eve of admission, the symptoms worsened, including prostration, asthenia, fever, vomiting, and a new episode of lipothymia, and he went to the emergency room. Upon observation, the patient was alert, confused, prostrate, feverish, dehydrated, normotensive (BP: 110/50 mHg), pulse 76 bpm, arrhythmic. Pulmonary auscultation did not reveal any changes; the abdomen was diffusely painful, without organomegaly and negative Murphy's test. There was no edema of the lower limbs and the neurological exam was normal.

The laboratory detected only mild macrocytic

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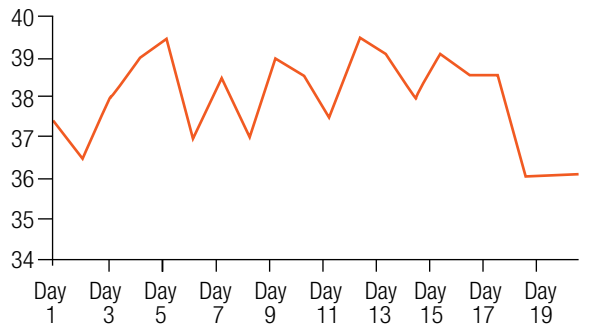

Temperature chart.

FIG. 1

anemia (MCV – 108 fL) with Hg of 10.3 gr/dL. The leukogram, ESR, platelet count, biochemistry, and urine II were all within the reference values. The thorax teleradiography was normal and the ECG showed only nonspecific alterations in ventricular repolarization.

He was admitted with a probable clinical diagnosis of a urinary infection and dehydration, and treated with ampicillin and gentamicin, following collection of samples for blood and urine cultures. On the fourth day of hospitalization, he still had a high fever and prostration. Pancytopenia was detected with: erythrocytes – 2,340,000/mm^3, leukocytes – 2300/mm^3, platelets – 87,000/mm^3. The initial culture exams were negative. There was no previous history of ingestion of drugs with potential medullary or peripheral toxicity for the hematopoietic series. Following the collection of samples necessary for cultures and serological exams, and the completion of a myelogram, the current antibiotic therapy was suspended, and a neutropenic antibiotic regimen with piperacillin, norfloxicin, and amikacin was initiated. Bacteriological cultures, including BK, were negative. Serology for hepatitis B and C, HIV, parvovirus, mononucleosis, CMV, and respiratory and enteric viruses were negative. The myelogram performed on the fifth day showed bone marrow rich in elements of parenchyma, myeloid hyperplasia, and a moderate shift to the left of the maturation curve of this series, with a slight increase in the number of myeloblasts (3%) and several maturation asynchronisms. The other series did not reveal any maturation alterations. There was no infiltration of abnormal elements. Sideroblasts were not observed. Iron deposits were unchanged. The bone biopsy, performed on the eighth day, revealed bone marrow with a generally preserved normocellular structure, with the presence of elements of the three hematopoietic series, with mild dysmorphia and a slight "shift to the left" in the red blood cell count, and mild dysmorphic features in the megakaryocytic count. Several precursor elements were observed in the white blood cell count, with central localization in the intratrabecular spaces, as well as a slight increase in the number of eosinophils. Several small lymphocytic aggregations without any preferential location were also noted. The iron deposits were slightly increased, without accentuation by reticulin staining. On the thirteenth day of hospitalization and the ninth day of the triple antibiotic regimen referred to above, the patient remained feverish, prostrated, and complained of headaches and reduced visual acuity. Anemia of 9.8 gr/dL and ESR over 140 mm persisted. A hypothesis that this was a GCA was proposed, given its frequent association with PMR and the fact that it can present as only a febrile syndrome. An ophthalmological exam was performed revealing bilateral pallor of the optical disk consistent with arteritis of the central retinal artery. Therapeutic window was applied for one day, for the collection of new blood and urine samples for culture exams. We continued cautiously with corticosteroid therapy (methylprednisolone, at a dose of 30 mg).

By the third day of this treatment, the patient was afebrile (*Fig. 1*), which unquestionably supported the clinical diagnosis of GCA. Unfortunately, it was not possible to perform a temporal artery biopsy for histological confirmation. He was discharged to our regular clinic with a diagnoses of GCA and PMR; MDS(?).

One month following discharge, the patient reported marked asthenia and anorexia. He had a fever and pallor, and auscultation detected disperse crepitations in both sides of the chest. The thorax teleradiography revealed heterogeneous hyperdensity of both lung bases. He was readmitted with a diagnosis of pneumonia. The hemogram results at this point were: RBC 3,050,000/mm^3; HG 12.0 gr/dL/ HTc 34.5%; platelets 192,000/mm^3; WBC 35,000/mm^3 (N 51%; L 26%; E 0%, B 0%; M 12%). The peripheral blood smear showed 2% myeloblasts, 1% promyelocytes, 3% myelocytes, 5% metamyelocytes, and neutrophils with hyposegmentation of the nuclei

TABLE I

Humoral	Cellular
Polyclonal hypergammaglobulinemia	Lymphopenia (↓ no. of T cells)
Hypogammaglobulinemia	CD4/CD8 inversion
Monoclonal gammopathy	Change in T cell response to mitogens
Non-agglutinating red cell antibodies	Change in production of INFg in vitro
	Change in B lymphocyte function
	↓ no. and functional immaturity of NK cells
	Functional changes in the monocyte-macrophage lineage (↓ capacity to recognize and present antigens, change in response to lymphokines)

and hypogranulation. The leukocyte alkaline phosphatase was normal, and the test for the Philadelphia chromosome was negative. Another myelogram was performed that showed bone marrow with normal cellularity, without abnormalities in the relationship between leukocytes and erythroblasts. There were sporadic signs of dyserythropoiesis (lobulated nuclei) in the erythrocyte series. In the granulocyte series, there was a left shift in the maturation curve due to an increase in myeloblasts and promyelocytes (15% of the total cellularity). There were also clear signs of dysgranulopoiesis (hypogranulation and hyposegmentation of the neutrophil nuclei). The megakaryocyte count was normal. Perl's staining revealed normal hemosiderin deposits, and rare occurrences of sideroblasts and siderophages. To summarize, it was a case of normocellular bone marrow with signs of myelodysplasia, with 15% myeloblasts and promyelocytes, consistent with MDS – RAEB. The patient was treated with ampicillin and gentamicin, resulting in significant clinical improvement, with apyrexia and the disappearance of general symptoms, while the radiological images continued to indicate leukocytosis. He was discharged to the regular clinic of the Hematology division of our outpatient clinic with a final diagnoses of PMR, GCA, and RAEB.

Discussion

GCA is a panarteritis that affects the temporal artery, other branches of the carotid artery, and less frequently, other arteries. Clinically, it is characterized by varying degrees of myalgia, arthralgia, cephalagia, claudication of the mastication muscles, and alterations in vision, but sometimes the only symptom is fever, as was the case with our patient. Its association with PMR has been recognized for several decades.[1] The characterization and differentiation of T cells are important factors in the progression of PMR to GCA. In patients with PMR, a clone of CD4 T lymphocytes, which exists in giant cell arteritis and is a key factor in determining the development of the phenomenon of vasculitis, does not develop.[3] These diseases are more commonly seen in elderly patients, with unknown etiopathogenesis, although genetic and immunological mechanisms are often involved. Recently, the association has been described between MDS, which is also more common among older patients, and various rheumatological situations,[4] in particular PMR,[1] as was the case with our patient, who also had GCA.

MDS encompasses syndromes of hematopoietic dysfunction in which a change in stem cells leads to abnormalities in the processes of cell maturation and differentiation, which in turn, lead to the occurrence of peripheral cytopenias, with normal or hypercellular bone marrow and a high probability of leukemic transformation. These diseases typically affect people over sixty years of age, with similar prevalence in males and females. So far, five types of MDS have been defined: refractory anemia, refractory anemia with ring sideroblasts, refractory anemia with excess blasts (the type found in our patient), chronic myelomonocytic leukemia, and refractory anemia with excess blasts in transformation. The most common initial form of presentation is anemia, but in 10 to 15% of cases it is infection and/or hemorrhagic dyscrasia.

Changes in cellular and humoral immunity have been demonstrated in MDS (Table I), with compromised cellular immunity playing a key role. Among the key changes, we highlight the existence of lymphopenias, an inversion in the CD4/CD8 relationship, a change in the production of INFgamma in vitro, a reduction in the number and functional maturity of NK cells, as well as functional changes in the monocytic-macrophagic lineage (reduction of the capacity to recognize and present antigens, change in the response to lymphokines). According to data in the literature, the absolute value of T cell

subpopulations (CD3+, CD4+, and CD8+) could have implications for the prognosis of MDS, i.e. the lower the counts of these populations, the worse the prognosis.[5] Among alterations in humoral immunity, we highlight polyclonal hypergammaglobulinemia, with an increase in levels of IgA and IgG.[6]

The existence of these immunological changes in MDS has led some authors to associate this fact with the coincidence of autoimmune diseases and phenomena during the course of these syndromes,[4] in particular pernicious anemia, hypothyroidism, seronegative rheumatoid arthritis, ulcerative colitis, immune vasculitis, and others.[6,7] Changes in the medullary nuclear microenvironment, with a spectrum of resulting immunological and clinical consequences, could favor the expression of rheumatological diseases,[4] such as PMR. Kohli and Bennett reported three cases of the latter association.[1] Altered lymphocytes and monocytes released lymphokines that produced changes in the target organs, namely in the vascular endothelium, skin, peripheral nerves, and synovial membrane.[2] This may be one of the several physiopathological mechanisms involved in the associations referred to.

In most of the cases described, as well as in our case, rheumatological manifestations preceded the onset of MDS and persisted during its evolution.[2] However, the interval between presentation of rheumatic disease and the diagnosis of hematological disease was variable.[4] This association is particularly common in patients with RAEB and RAEB-T, which by itself has a reserved prognosis, and there are some who believe that rheumatic manifestations in these patients is an indicator of poor prognosis.[2]

We believe that a sufficient number of cases of association between MDS and PMR have already been described to defend the view that it is more than mere coincidence. It is possible that more similar cases exist that have not yet been reported because clinics have not yet been alerted to this possibility. ■

References

1. Kohli M and Bennett. An Association of Polymyalgia Rheumatica With Myelodysplastic Syndromes. J Rheumatol 1994; 21: 1357-1359.

2. Castro M, Conn DL et al. Rheumatic manifestation in Myelodysplastic Syndromes. J Rheumatol 1991; 18: 721-727.

3. Weyand C and Jorg J. Molecular approaches toward pathologic mechanisms in Giant Cell Arteritis and Takayasu's arteritis. Current Opinion in Rheumatology 1995; 7: 30-36.

4. Kuzmich PV, George A, Karsh J. Rheumatic Manifestations in Patients with Myelodysplastic and Myeloproliferative Diseases. J Rheumatol 1994; 21: 1649-1654.

5. Colombat PH, Renoux M, Lamagnere JP, Renoux G. Immunologic Indices in Myelodysplastic Syndromes. Cancer 1988; 61: 1075-1081.

6. Mufti GJ, Figes A, Hamblin TJ, Oscier DG, Copplestone. Immunological Abnormalities in Myelodysplastic Syndromes. I Serum Immunoglobulins and Autoantibodies. Br J Hemat 1986; 63: 143-147.

7. Hamblin TJ. Immunological Abnormalities in Myelodysplastic Syndromes, chapt 8. The Myelodysplastic Syndromes. Edit by G.J Mufti; Da Galton – Churchill Livingstone-New York 1992: 97-114.