Hodgkin's disease manifesting through pyrexia of unknown origin

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Abstract

In Hodgkin's disease, the anatomical extension of the disease and the histological subtype are the major determinants on the presentation. Often, clinical and laboratorial manifestations are hardly specific and it is difficult to suspect the diagnosis. A clinical case is reported of lymphocyte depleted abdominal Hodgkin's lymphoma, presented initially with pyrexia of unknown origin, followed by successive clinical and laboratory abnormalities, which, despite their severity, were not specific enough to elicit an immediate diagnosis. A few of the less frequent forms of presentation of Hodgkin's disease are discussed, stressing the importance of being alert to the less typical manifestations of this disease.

Key words: case report, Hodgkin's disease, lymphocyte depletion, clinical manifestations, fever of unknown origin.

Introduction

Hodgkin's disease is a neoplasm of the lymphatic tissues that, although not very common, requires a systematic and multidisciplinary approach to its diagnosis, staging and treatment. For this reason, it has become a paradigm in Oncology, and is at the same time, one of the malignancies that have better chance of cure.

The anatomical extension of the disease, associated symptoms, and to a lesser extent, the histological subtypes, are the most common factors influencing the form of presentation, prognosis and therapeutic options.

This disease has an annual incidence of 3.2 cases in 100,000 people, predominantly affecting males and following a bimodal age distribution curve with a peak on the 3rd decade of life, and another at over 50 years.

Its most common clinical characteristics include the following:[1]

Most of the patients have painless, superficial, asymmetric adenopathies. Cervical lymph nodes are present in 60% to 70% of the cases, axillary nodes in 10% to 15% and inguinal nodes in 6% to 12%. Sometimes, the size of the adenopathy reduces and increases spontaneously. Retroperitoneal lymph nodes are also commonly involved, but usually the diagnosis is reached only through computed tomography (CT scan).

Palpable splenomegaly occurs in 50% of patients during the course of the disease. In rare instances, the enlarged spleen is very accentuated. The liver may also be enlarged with hepatomegaly.

Mediastinal involvement can occur from the onset in 6% to 11% of the patients, particularly in young women with the nodular sclerosis subtype. Associated pleural effusion or obstruction of the upper vena cava can occur.

Hodgkin's disease of the skin can occur as a late complication in 10% of patients. Other organs (digestive tract, bones, lungs, spine or brain) may also be involved from the onset, although this is rare.

Constitutional symptoms are prominent in the cases of disseminated disease, and may include: fever in 30% of the patients, which may be continuous or cyclical (Pel-Ebstein fever, which is virtually pathognomonic); generalized, sometimes severe itching, in 25% of the cases; complaints of pain, induced by alcohol, in the involved areas; weight loss; night sweat; asthenia; fatigue; anorexia; and cachexia.

This paper presents a clinical case of Hodgkin's

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TABLE I

Summary of the analytical results obtained before hospitalization and upon admission

	Tondela 1	On admission
Erythrocytes T/1		1.84
Hemoglobin g/dL	10.7	4.9
Hematocrit L/T		14.2
Average globular volume fl	70	77.1
Leukocytes G/L	8.4[2]	7.4
Platelet G/L	345	141
Prothrombinemia %	66	69
ESR mm/h	65	24.2
C-reactive protein mg/dL		24.2
Creatinine mg/dL	0.6	0.8
Total protein g/dL	5.2	4.3
Albuminaemia g/dL		1.5
Total Bilirrubinemia mg/dL	0.3	1.0
Direct Bilirrubinemia mg/dL		0.4
Aspartate transaminase U/L	97	12
Alanine transaminase U/L	85	14
Gamma-glutamyl transpeptidase U/L	133	48
Alkaline phosphatase U/L	979[3]	291[4]
Lactate dehydrogenase U/L	530	386

[1]16 days before hospitalization at HUC
[2]With 93% of neutrophils
[3]Normal count < 300 U/L (laboratory of Hospital de Tondela)
[4]Normal count < 120 U/L (laboratory of HUC)

disease that manifested itself as febrile syndrome of prolonged evolution, accompanied by successive clinical and laboratory anomalies, the interest of which lies in the difficulties related to its diagnosis and in a rapidly fatal, aggressive course.

Case report

Male patient, 33 years old, single, born and living in Tondela, a laborer (last occupation in road construction).

One month prior to hospitalization, the patient complained of chest and posterior neck pain, which was sometimes disabling; high temperature; anorexia; asthenia; weight loss; and nausea, resulting in the patient being confined to bed, prostrated and not very communicative.

When hospitalized at Hospital de Tondela, the patient had febrile peaks every afternoon, despite treatment with erythromycin (for one week), followed by amoxicillin and clavulanic acid, and isoniazid, rifampicin, pyrazinamide and streptomycin. Towards the end of the second week of hospitalization, treatment with naproxen was begun, resulting in fever disappearing for three days. The fever later returned, and the patient was transferred to the Hospitals of Universidade de Coimbra (HUC).

The patient's history included severe bilateral hypoacusis since childhood, and more than one year prior to hospitalization, the patient had been diagnosed with pulmonary tuberculosis (in France), having received anti-tuberculosis therapy for one year until around two months prior to hospitalization.

When admitted to the hospital, the patient had lost weight and was not reacting normally. He was pale and apyretic. Pulse rate was 80 ppm, and blood pressure was 130-60 mmHg. Pulmonary auscultation did not reveal any changes, and heart auscultation revealed a systolic murmur. No changes were observed on abdominal examination, and palpable peripheral adenopathies were not observed.

Additional analytical tests upon admission are listed in *Table I*. X-ray of the chest did not reveal any changes.

The therapy was maintained, and two units of red blood cells (RBC) were administered. A slight improvement was observed in the patient's general condition, however fever peaks between 38º and 39º recurred until the 7th day of hospitalization, during which period the anemia became worse, requiring new transfusion of RBC; severe thrombocytopenia and lymphocytopenia appeared (*Tables II and III*). In sternal puncture, it was not possible to aspirate the bone marrow.

Between the 8th and 10th day of hospitalization, marked jaundice and right-sided pleural effusion, accompanied by hypotonia and intense prostration developed. Diagnostic thoracentesis revealed a fluid with characteristics of an exudate (pH = 7), containing inflammatory cells with predominance of lymphocytes, and ADA determination = 5.

An abdominal echogram revealed: splenomegaly (14.3 x 13 x 11 cm) of heterogeneous texture due to

TABLE II

Summary of the analytical results obtained on days 7, 9 and 11 of hospitalization

Erythrocytes T/1	2.25	3.08	2.50
Hemoglobin g/dL	6.2	9.0 1	7.5
Hematocrit L/T	18.2	25.5	20.4
Average globular volume fl	80.8	82.8	81.6
Leukocytes G/L	6.30	6.70	10.30
Neutrophils %	84	89.4	
Eosinophils %	2	1	
Basophils %	0	0	
Lymphocytes %	4	3.6	
Monocytes %	6	6	
Platelet G/L	90	35	12
Prothrombinemia %		52	34
ESR mm/h		64	81
Creatinine mg/dL		1.0	1.8
Total protein g/dL		3.6	3.7
Albuminemia g/dL		1.9	2.0
Total Bilirubinemia mg/dL		17.0	29.7
Direct Bilirubinemia mg/dL		14.9	22.9
Aspartate transaminase U/L		56	74
Alanine transaminase U/L		27	39
Gamma-glutamyl transpeptidase U/L		29	16
Alkaline phosphatase U/L		397	327
Lactate dehydrogenase U/L		411	580

1 After transfusion of 2 units of RBC on the 7th day.

the presence of hyperechogenic nodule formation in the lower third, measuring 2.1 cm; adenopathies within the hepatoduodenal ligament (the largest with 1.5 cm); moderate volume peritoneal effusion; right-sided pleural effusion; small pericardial effusion.

Serology for toxoplasmosis, ESR, EBV, Brucella, Salmonella, Coxiella, Borrelia, HIV-1 (antibody and antigen), HIV-2, HBV and HCV, and VDRL reaction were negative. Anti-CMV IgM antibody was at the threshold for positivity.

On the 11th day of hospitalization, the patient had

TABLE III

Lymphocyte count

Total lymphocytes	300/mm^3
CD 19 (B4)	10%
CD 2 (Pan T)	68%
CD 4 (T helper)	16%
CD 8 (T suppressors/cytotoxic)	36%
T4 / T8	0.44
B (abs)	30/mm^3
Pan T (abs)	204/mm^3
T helper (abs)	48/mm^3
T suppressors/cytotoxic (abs)	108/mm^3

dyspnea, marked asthenia, marked jaundice, extensive right-sided pleural effusion, and painful, rigid, tense abdomen, defensive on palpation and with bowl sounds. Analytical examination (*Table II*) revealed new aggravation of anemia, lymphocytopenia and thrombocytopenia, hyperbilirubinemia and changes compatible with consumption coagulopathy.

A CT scan was performed, revealing (in a preliminary report): large right-sided pleural effusion with collapsed right lower lung; homogenous hepatomegaly without dilatation of the bile ducts; heterogeneous splenomegaly with multiple small hypocontrast regions; delayed excretion from both kidneys. RBC, plasma and platelets were administered; the anti-tuberculosis drug and another antibiotic were suspended; therapy with imipenem/cilastine was begun. The hypothesis of a lymph proliferative disease was considered, for which therapy with prednisolone 1g/day was initiated.

The culture of the sputum collected on this date was positive for Candida albicans and Klebsiella pneumonia, with antibiogram revealing sensitivity for most of the tested antibiotics, including amoxicillin/clavulanic acid and imipenem.

On day 12, the patient was restless, apyretic, and dehydrated; he had intense jaundice; abundant rales on the right pulmonary field above the effusion and aortic systolic ejection murmur was heard; the abdomen was rigid and painful on palpation, with frequent sounds of normal volume. Needle bone biopsy and chest drainage were performed, in which

400 cc of pleural fluid was collected. The above described analytical changes continued, associated with hypoxemia and hypocapnia.

Chest X-ray revealed reduced transparency of the right pulmonary region in relation to the parenchymal inflammatory changes; pleural effusion; a type of mass adjacent to the right surface of the heart, leading to a change in the morphology of the mediastinal shadow (requiring a CT scan, which was not performed), but that was not confirmed in subsequent radiograms.

On day 13, the patient's general condition had deteriorated and a state of confusion was observed; the abdomen was less painful and more depressed, and liver was palpable (rigid, 6cm below costal margin); splenomegaly was observed. The patient was administered RBC and cryoprecipitate, and therapy with amphotericin B and metronidazole was begun.

On day 14, the patient was dehydrated, with multiple organ failure, severe anemia and signs of respiratory difficulty, and was referred to the Intensive Care Unit.

A tracheobronchial aspiration identified Aspergillus fumigates. Bacteriological examination of the pleural fluid, which presented a predominance of lymphocytes, was negative. Chest X-ray revealed aspects of consolidation of the air space throughout the right lung, suggestive of pneumonia.

Therapy with imipenem, metronidazole and amphotericin B, and RBC, fresh plasma and platelet transfusions were maintained, as well as ventilation and hemodynamic support. CT scan of the abdomen reported hepatosplenomegaly, including heterogeneous spleen with multiple small hypodense nodules, the largest in the lower region, which was highlighted with contrast; the kidneys had delayed excretion, particularly the right kidney, but with normal morphology; heterogeneity of the right iliopsoas (upper portion); left lateral aortic adenopathy.

On day 16 of hospitalization (day 3 at the ICU), the patient was submitted to exploratory laparotomy, which revealed: ascites of approximately 2000 cc; homogenous hepatomegaly; splenomegaly without signs of abscess; absence of abscess or retroperitoneal cellulitis or psoas; multiple mesenteric adenopathies; hard, white, nipple-shaped sarcomatous lesions involving the ileum, around 10 cm from the ileocaecal valve, occupying around 15 cm of the intestine and resulting in almost a complete occlusion of the lumen. Splenectomy and right hemicolectomy with distal ileostomy were performed. An intra-operatory biopsy of the liver was also performed, but the specimen was not referred to the Pathological Anatomy Service.

On day 18, an abdominal ultrasound identified heterogeneous collection in the spleen cavity compatible with clotting; surgical revision of the hemostasis was performed.

In the following days, the patient was hemodynamically instable and did not require mechanical ventilation; on X-ray examination, extensive pneumonia involving virtually all of both lungs was observed.

On day 27 of hospitalization, the patient had upper gastrointestinal bleeding and the endoscopy revealed: extensive ulcers in the distal esophagus, none of them with signs of recent hemorrhage; epistaxis and fresh blood in the oropharynx, running continually down through the esophagus.

On day 30, the patient had generalized edemas, dehydration, distended and rigid abdomen.

A first analysis from the anatomical-pathological examination of the specimen suggested a granulomatous disease. Bone biopsy revealed marked bone marrow fibrosis. The patient died on day 32 of hospitalization, after 18 days in the intensive care unit. Anatomical-clinical autopsy was not authorized.

Histological assessment of the specimen revealed: mesenteric lymph nodes with non-caseating, necrotising granulomas and without Langhans' giant cells, involving all nodes investigated. In the preserved pulp, lymphoid depletion was observed, as well as the presence of several plasma cells, some eosinophils and a population of bizarre Sternberg-Reed (S-R) cells with multiple nuclei, mummified cells and Hodgkin's cells. Surrounding these elements, there were fibrillary fibrosis and hyaline.

Hodgkin's and S-R cells presented CD30 and negativity for LCA, CD20 and CD3. Only CD15 stained the granulocytes. The accompanying lymphoid population was positive for CD20 and CD3.

Spleen: Splenic parenchyma with several necrotising granulomas, hemorrhagic areas and vessels with hyalinised walls and hyaline necrosis. Focally, some bizarre cells were observed, with morphological and immunohistochemical aspects, which were similar to those described previously.

Small and large intestine: on macroscopy, in the ileum, 8cm from the ileocaecal valve, a segment with saccular dilation was observed, 6cm at its longest axis, covered with ulcerated mucosa and a greenish

membrane, delimited by a thick intestinal wall (reaching 1.5 cm).

On microscopy, the terminal ileum had areas with ulcerated mucosa and parietal fibrosis. This had lymphoid aggregates, necrotising granulomas, endarteritis of the vessels and vascular thrombosis, and focally, vasculitis.

Investigations for microorganism (through the Ziehl-Neelson, P.A.S., Grocott, Gram and Giemsa techniques) and CMV were negative.

Histopathological diagnosis: lymphoid depletion type Hodgkin's lymphoma, involving mesenteric lymph nodes and the spleen.

Discussion

This is a clinical case of Hodgkin's disease with a rare presentation form and aggressive behavior, resulting in diagnostic difficulties and a rapid and fatal course, which did not allow for a specific therapeutic intervention.

Usually, Hodgkin's disease develops with peripheral painless adenopathy above the diaphragm, and it may be associated with constitutional symptoms, such as fever and weight loss (symptoms B), in around 30% of the patients,[2] particularly in the elderly or people with advanced disease, as was this case. The lymphoma follows an extension pattern, involving groups of adjacent axial lymph nodes.

Patients with mixed cells or the lymphoid depletion subtype tend to develop to the most advanced stage of the disease and have symptoms that include weight loss, fever and sweating, but without peripheral or prominent mediastinal adenopathies, and usually with extensive intra-abdominal disease, particularly hepatomegaly and splenomegaly.[3,4]

Nevertheless, the involvement of mesenteric lymph nodes is rare, as is as the appearance of primary extranodal involvement of the bones, digestive tract and brain.[5]

In fact, primary abdominal Hodgkin's disease with hepatomegaly, splenomegaly and extensive adenopathies occurs less frequently, and in these circumstances, ruling out other neoplasms is recommended, particularly non-Hodgkin's lymphoma[2] which, although rare, might be difficult to diagnose due to the existence of a combined Hodgkin's and non-Hodgkin's lymphoma.[4]

This patient had mesenteric and splenic Hodgkin's disease, which initially manifested through a condition of fever associated with weight loss and deterioration of the general condition.

It is important to mention that Hodgkin's disease is often accompanied by a granulomatous process that may involve extranodal organs, but without the diagnosed histological characteristics,[5] a process that seems to have occurred in the terminal ileum of this patient.

Some patients with extensive abdominal and peripherally scarce adenopathies are initially investigated due to fever of unknown origin and usually develop the mixed cell or lymphoid depletion subtypes.[2]

Cases with abdominal involvement due to the development of the disease experience abdominal pains, intestinal perturbations, and sometimes ascites.[2]

The patients with advanced and refractory disease suffer from marked anorexia, fatigue, weight loss, fever and night sweating.[4]

This patient also had important laboratory anomalies. In Hodgkin's disease, these anomalies are usually non-specific. They may include inflammatory anemia, granulocytosis, eosinophilia, thrombocytosis or absolute lymphocitopenia,[6] this typically in a more advanced stage.[2]

The existence in this patient of severe anemia, thrombocytopenia and lymphocytopenia, associated with granulocytosis and coagulation changes led to a hypothesis of mixed pathophysiology of medullary invasion (although bone marrow biopsy revealed only intense fibrosis), hypersplenism (as there was splenomegaly invading the organs) and autoimmune characteristics (based on the reduced red blood cell and platelet counts after each transfusion).[6]

The increase in the sedimentation rate, which was accentuated and remained unchanged in this patient, has a prognostic significance, correlating with advanced disease and constitutional symptoms.[6]

The alkaline phosphatase levels may be generally increased in limited disease, or may be associated with liver, bone or marrow involvement. On the other hand, prominent laboratory anomalies are observed in rare forms of presentation. These include abnormal hepatic evidence from voluminous adenopathy, bile duct obstruction or intrahepatic cholestasis.[6]

Although there is no histological confirmation, the existence of hepatomegaly, marked increase in direct bilirubinemia, alkaline phosphatase and serum transaminase, as well as hypoalbuminemia and prolonged coagulation time, are likely to support the hypothesis

of hepatic invasion, pointing to a predominantly cholestatic and intrahepatic condition.

Nevertheless, malabsorption etiology for hypoalbuminemia and coagulopathy (invasion of the distal large intestine) cannot be ruled out, particularly because an immune phenomenon may coexist with the latter.

In fact, Hodgkin's disease is associated with several immune defects: reduced delayed skin hypersensitivity; reduced natural-killer cytotoxicity; increased T-cells and monocyte suppressing activities; higher levels of circulating immune complexes, with increased production of immunoglobulins; production of anti-lymphocyte and anti-la antibodies; reduction of the T-cell proliferative responses to mytogenic stimulation; reduction of lymphokine production.[6] Inversion of the CD4/CD8 ratio may also occur.[2]

In several studies, the reduction of the immunological reactivity correlates with advanced stages of the disease and the presence of systemic symptoms, and not with the prognosis. Clinically, there is increased incidence of herpes zoster, cytomegalovirus, fungal infections (cryptococcosis, candidiasis) and tuberculosis,[1] and appearance of warts, but not of opportunistic infections.[2]

In this patient, the absolute lymphocytopenia was remarkable, with a sharp reduction in CD4 count and complete inversion of the CD4/CD8 ratio, which resulted in prolonged suspicion of HIV infection).

In this case, bacterial and fungal infections were detected and the personal history included tuberculosis, but no relationship was established with underlying immune deficiency.

In relation to the natural history, which was addressed at the beginning of this paper, it can be summarized that the lymphoid depletion subtype, which affected this patient, had already spread when the diagnosis was reached, and it predominantly affects elder patients who usually have systemic symptoms and poorer prognosis, particularly associated with fever and weight loss.

Conclusion

A case of lymphoid depletion type Hodgkin's disease was presented, with clinical and development characteristics matching the commonly known descriptions of the disease. Nevertheless, due to its rarity and the absence of localized pathology signs, even on imaging scans, a timely diagnosis was not possible.

It is hoped that the presentation of this clinical case will facilitate the establishment of more powerful diagnostic strategies before similar conditions evolve, particularly when there are alarming signs such as severe symptoms and laboratory changes, as observed in this patient. ■

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