World Journal of Surgery and Surgical Research

Case Report
Published: 16 Sep, 2024

# Hemophagocytic Lymphohistiocytosis Revealing Prostate Adenocarcinoma: A Case Report

*Dergaoui H*, Barkat K, Al Awati M, Yahyaoui H, Ait Ameur M and Chakour M*

*Hematology Laboratory, Avicenne Military Hospital, Marrakech, Morocco*

## Abstract

Hemophagocytic Lymphohistiocytosis (HLH) is a state of hyperinflammation resulting from an overproduction of pro-inflammatory cytokines, leading to the activation of macrophages that ingest the blood components (red blood cells, leukocytes, platelets). HLH is categorized into primary and secondary forms. Primary HLH is associated with a primary immune deficiency, while secondary HLH is related to various pathological conditions, including neoplastic diseases, infections, and autoimmune diseases. Solid tumors are rarely associated with HLH, accounting for only 1% of cases, mainly in the presence of bone marrow metastases, a relationship that is seldom documented in the literature through isolated cases. We report here a case of HLH revealing prostate cancer with bone marrow metastasis in a 58-year-old patient. HLH is a serious condition with a high mortality rate, due to an inappropriate immune response. Targeted etiological treatment is essential and may be effective in certain situations.

**Keywords: Hemophagocytic lymphohistiocytosis; Prostate adenocarcinoma; AST**

## Introduction

The term "histiocytosis" defines a group of pathologies characterized by the proliferation and accumulation of macrophages. The designation "Hemophagocytic Lymphohistiocytosis" (HLH) specifically refers to macrophage-related histiocytoses [1]. It is essentially a chronic inflammatory reaction resulting from an increased secretion of pro-inflammatory cytokines due to abnormal activation of the immune system. It is important to differentiate between primary HLH, which is related to congenital immune disorders, and secondary HLH, which can be triggered by neoplastic diseases, infections, autoimmune diseases, or cancers. The high mortality rate associated with HLH makes the rapid recognition and treatment of this syndrome essential. Unfortunately, its diagnosis is challenging and relies on numerous clinical and biological criteria that, in isolation, are not specific to the disease [2]. It is the combination of these signs that will raise suspicion for the diagnosis of HLH [3,4].

Given the absence of specific characteristics, several diagnostic scores have been developed, among which the HScore includes nine clinicobiological criteria: Underlying immunosuppression, fever, organomegaly, number of cytopenias, levels of ferritin, triglycerides, fibrinogen, AST, and the presence of hemophagocytosis [5]. A bone marrow examination is then recommended to confirm the presence of hemophagocytosis. The total score achieved is subsequently converted into the probability of developing a hemophagocytic syndrome [6].

## Observation

This is a 58-year-old man, a smoker with hypertension, without a family history of neoplasia. He was admitted to the emergency department due to altered consciousness and acute respiratory distress requiring immediate assisted ventilation, all occurring against a backdrop of general health deterioration with a fever measured at 39°C.

Physical examination revealed splenomegaly extending beyond the umbilicus and two painful, hard, mobile left inguinal lymphadenopathies. Biological tests showed bicytopenia on the complete blood count, characterized by normochromic normocytic arylative anemia and thrombocytopenia. Coagulation tests suggested moderate disseminated intravascular coagulation, evidenced by a decreased prothrombin level, prolonged activated partial thromboplastin time, increased D-dimer levels, and hypofibrinogenemia.

Biochemical analysis indicated hepatic cytolysis, increased Lactate Dehydrogenase (LDH),

OPEN ACCESS

***Correspondence:***
*Dergaoui Hanane, Hematology Laboratory, Avicenne Military Hospital, Marrakech, Morocco,*

**Received Date**: *26 Aug 2024*
**Accepted Date:** *11 Sep 2024*
**Published Date:** *16 Sep 2024*

***Citation:***
*Dergaoui H, Barkat K, Al Awati M, Yahyaoui H, Ait Ameur M, Chakour M. Hemophagocytic Lymphohistiocytosis Revealing Prostate Adenocarcinoma: A Case Report. World J Surg Surgical Res. 2024; 7: 1570.*

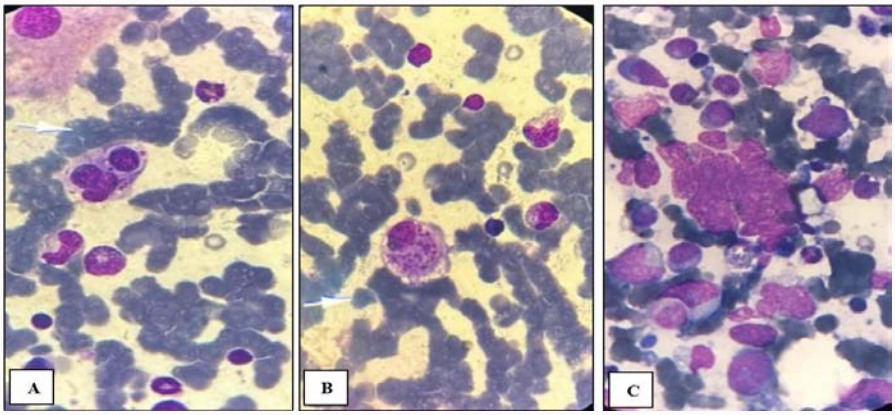


**Figure 1:** Myelogram obtained after bone marrow aspiration and spread, MGG staining (objective x1000)
A, B) Hemophagocytosis: Macrophage engulfing hematopoietic cells. C) Clusters of extra-hematopoietic cells.

**Table 1:** Biological parameters of the patient during hospitalization.

| | 1st day | 5th day | 10th day |
|---|---|---|---|
| White blood cells (4-10,000/mm³) | 5,000 | 4,900/mm³ | 2,170/mm³ |
| Neutrophils (1,500-7,000/mm³) | 2,800 | 3,000/mm³ | 1,100/mm³ |
| Hemoglobin (12-18 g/dL) | 4.6 | 6.2 g/dL (post-transfusion) | 8.7 g/dL |
| Platelets (150,000-400,000/mm³) | 69,000 | 65,000/mm³ | 57,000/mm³ |
| Schistocytes | - | - | 1.5% |
| LDH (135-225 U/L) | 749 | - | 965 |
| ASAT (<35 UI) | 128 | 249 | 694 |
| ALAT (<45 UI) | 63 | 82 | 102 |
| Bilirubin T/D (<17/<4 µmol/L) | 30/26 | 32/27.7 | 70/65 |
| Ferritin (30-400 ng/mL) | 1,800 | >2,000 | >2,000 |
| Triglycerides (<1.7 mmol/L) | - | 3.2 | 3.4 |
| Total Cholesterol (3.6-5.2 mmol/L) | - | 2.98 | - |
| CRP (<10 mg/L) | 56 | 30 | 32 |
| Procalcitonin (ng/mL) | 1 | - | 3.5 |
| Sodium (136-145 mmol/L) | 134 | 138 | 132 |
| TP (>80%) | 65% | 61% | 52% |
| Fibrinogen (2-4 g/L) | 1.3 | - | 1.4 g/L |
| D-dimers (<ng/ml) | 800 | - | 5 |
| Ca19-9 (<27 U/mL) | - | - | 987.5 |
| Vit B12 (141-489 pg/mL) | - | - | 1,930 |

hyperferritinemia, and hypertriglyceridemia alongside elevated total cholesterol levels. Serological tests were requested; HBsAg-HBsAb, anti-HBc, anti-HCV, and anti-HIV (1+2) pairs returned negative, while Epstein-Barr virus serology suggested a past infection. An infectious disease workup was initiated, revealing elevated C-reactive protein and normal procalcitonin levels (Table 1).

The analyzed blood smear shows the presence of globular anisocytosis with a few schistocytes (1.5%) and the absence of young or atypical cells. The bone marrow examination performed on our patient reveals a very rich marrow with numerous activated macrophages and multiple instances of hemophagocytosis, as well as many extra-hematopoietic cells organized into clusters (Figure 1).

The measurement of tumor markers indicates an elevation of PSA to 480 ng/ml. A prostate MRI identified a lenticular lesion in the right PZPM region, classified as PIRADS 5. An endoscopic examination with biopsy was performed, revealing the presence of an acinar prostate adenocarcinoma with a Gleason score of 9 (5+4), classified as Group 4 by ISUP, infiltrating 60% of the examined surface in the right lobe and 40% in the left lobe. The patient passed away two days after the diagnosis of the tumor was made.

## Discussion

The LHH is characterized by a state of hyperinflammation, although its pathophysiology is not yet fully understood. All studies have concluded that there is an existence of a "cytokine storm" involving both lymphocytes and macrophages, which is responsible for the various clinical and biological disorders observed.

At the first pathophysiological level, Tumor Necrosis Factor α (TNF-α) is capable of inhibiting lipoprotein lipase, leading to an increase in triglycerides; Interleukin 18 (IL-18) may trigger apoptosis of hepatocytes, as well as hematopoietic stem cells; and interferon gamma activates phagocytosis and may also lead to myelosuppression, not to mention a procoagulant activity.

At a second pathophysiological level, Hemophagocytic Lymphohistiocytosis (HLH) represents a common final pathway of primary immune deficiencies, lymphoproliferative syndromes, certain infections, and even terminal cancers, especially when there were medullary metastases. A recently discovered mechanism is the over-activation of the inflammasome due to an activating mutation (described for the NLRC4 gene), leading to hemophagocytic syndrome independently of T lymphocytes.

The diagnostic criteria for HLH have been redefined by an international panel of specialists. The HScore, somewhat complex, is used for both the diagnosis and the risk of early death from secondary HLH. It comprises nine criteria, three of which are clinical: Context of immunosuppression, fever, organomegaly; five are biological: Triglycerides, ferritin, Aspartate Aminotransferase (AST or Serum Glutamate-Oxaloacetate Transaminase [SGOT]), fibrinogen, and cytopenia; and one is cytological: Hemophagocytosis on the bone marrow aspirate, as illustrated in Table 2. For values ranging from 0 to 250, the authors consider that the best diagnostic threshold is at a value of 169, which has a sensitivity of 93% and specificity of 86%, allowing for accurate classification of 90% of patients. Our patient had an HScore of 243.

**Table 2:** Probability of diagnosing secondary Hemophagocytic Lymphohistiocytosis (HLH) based on clinical presentation and biological and cytological results: HScore [5,7].

| Parameter | No. of points (criteria for scoring) |
|---|---|
| Known underlying immunosuppression* | 0 (no) or 18 (yes) |
| Temperature (°C) | 0 (<38.4), 33 (38.4-39.4), or 49 (>39.4) |
| Organomegaly | 0 (no), 23 (hepatomegaly or splenomegaly), or 38 (hepatomegaly and splenomegaly) |
| No. of cytopenias† | 0 (1 lineage), 24 (2 lineages), or 34 (3 lineages) |
| Ferritin (ng/ml) | 0 (<2,000), 35 (2,000-6,000), or 50 (>6,000) |
| Triglyceride (mmoles/liter) | 0 (<1.5), 44 (1.5-4), or 64 (>4) |
| Fibrinogen (gm/liter) | 0 (>2.5) or 30 (≤ 2.5) |
| Serum glutamic oxaloacetic transaminase (IU/liter) | 0 (<30) or 19 (≥ 30) |
| Hemophagocytosis features on bone marrow aspirate | 0 (no) or 35 (yes) |

*Human immunodeficiency virus positive or receiving long-term immunosuppressive therapy (*i.e.*, glucocorticoids, cyclosporine, azathioprine)
†Defined as a hemoglobin level of ≤ 9.2 gm/dl and/or a leukocyte count of ≤ 5,000/mm$^3$ and/or a platelet count of ≤ 110,000/mm$^3$

Signs of hemophagocytosis are visible in only 35% of cases at the time of diagnosis [8], and can be searched for and identified on a bone marrow aspirate, which is a key examination to confirm the diagnosis and establish, or even suggest, the origin of this syndrome. Generally, the bone marrow is rich and infiltrated by activated histiocyte-macrophages of normal appearance, which phagocytose hematopoietic cells, with a percentage exceeding 3% of nucleated cells [8].

Other biological abnormalities are frequently observed, including an aregenerative anemia accompanied by signs of hemolysis, hemostatic disorders such as hypofibrinogenemia or thrombocytopenia that may progress to disseminated intravascular coagulation [9,10], an elevation of LDH, signs of hepatic cytolysis, and hyponatremia.

HLH is secondary in more than 90% of cases and can manifest in the context of various pathologies. Among the underlying causes, neoplasms are one of the main etiologies, representing about 30% of cases [11]. High-grade lymphomas are the primary source, accounting for 20% of cases, followed by other malignant hematological disorders such as acute leukemias, multiple myeloma, myelodysplastic syndromes, and myeloproliferative syndromes. In only 1.6% of cases, HLH may also complicate or reveal a solid tumor, particularly in the presence of marrow metastases [11,12].

A literature review revealed only cases of gastric carcinoma, mediastinal germ cell tumors, and hepatocellular carcinoma [13]. However, the novelty of this case lies in the association of HLH with prostate cancer, which has been rarely described [14]. For our patient, no other secondary cause was identified aside from metastases. Blood cultures and viral serologies, including those for EBV and HIV, were negative. CRP was slightly elevated and procalcitonin was normal. However, there were no signs of blastosis, dysmyelopoiesis, or parasitic elements observed in the bone marrow aspirate. Furthermore, examinations demonstrated the presence of extra-hematopoietic cell images revealing prostate adenocarcinoma, along with an elevated PSA level.

## Conclusion

Hemophagocytic Lymphohistiocytosis (HLH) is a rare pathology that presents a high mortality rate, resulting from inappropriate activation of the immune system. The various associations described involve malignant hematological conditions, viral or bacterial infections, or even parasitic infections, rheumatic or autoimmune diseases, as well as drug reactions.

HLH has been reported quite infrequently (1%) and often in the context of advanced stages, associated with multiple types of solid cancers such as melanoma, breast cancer, pancreatic cancer, stomach cancer, and lung cancer. It may present initially, leading to a cancer diagnosis, or it can develop during treatment, exacerbated by chemotherapy that disrupts the immune response, in addition to the basal pro-inflammatory state induced by cancer, which likely facilitates the triggering of HLH during periods of added stress.

The diagnosis relies on a combination of clinical and biological signs that are non-specific, necessitating cytological or histological examination for hemophagocytosis and a fairly exhaustive etiological investigation.

Secondary bone localization of solid cancers, particularly prostate cancer, is especially dangerous because it is an "osteophilic cancer," due to the role played by bone tissue, which acts as a niche and a conducive environment for the hosting and adaptation of metastatic cells, thus promoting their tumor growth.

## References


1. Costello R, Venton G, Farnault L, Colle J, Baccini V. Lymphohistiocytose hémophagocytaire. EMC - Traité de Médecine Akos. 2022.
2. Thiebaut L, Pasquier G, Theret S, Russello J. Hemophagocytic lymphohistiocytosis: A retrospective analysis of 66 patients. Rev Méd Interne. 2024;45(1):6-12.
3. Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. Lancet. 2014;383(9927):1503-16.
4. Rivière S, Galicier L, Coppo P, Marzac C, Aumont C, Lambotte O, et al. Reactive hemophagocytic syndrome in adults: A retrospective analysis of 162 patients. Am J Med. 2014;127(11):1118-25.
5. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol. 2014;66(9):2613-20.
6. Papo T. Syndromes hémophagocytaires, syndrome d'activation des macrophages. EMC - Traité De Médecine. 2018;13(4).
7. Henter J-L, Elinder G, Ost A. Diagnostic guidelines for hemophagocytic lymphohistiocytosis. Semin Oncol. 1991;18(1):29-33.
8. Fukaya S, Yasuda S, Hashimoto T, Oku K, Kataoka H, Horita T, et al. Clinical features of haemophagocytic syndrome in patients with systemic

autoimmune diseases: Analysis of 30 cases. Rheumatology (Oxford). 2008;47(11):1686-91.

9. Wong KF, Chan JK. Reactive hemophagocytic syndrome – A clinicopathologic study of 40 patients in an Oriental population. Am J Med. 1992;93(2):177-80.

10. Kaito K, Kobayashi M, Katayama T, Otsubo H, Ogasawara Y, Sekita T, et al. Prognostic factors of hemophagocytic syndrome in adults: Analysis of 34 cases. Eur J Haematol. 1997;59(4):247-53.

11. Karras A, Hermine O. Syndrome d'activation macrophagique. Rev Med Interne. 2002;23(9):768-78.

12. Michot M, Hiéc M, Galicier L, Lambotte O, Michel M, Bloch-Queyratf C, et al. Le syndrome d'activation lymphohistiocytaire de l'adulte. (Hemophagocytic lymphohistiocytosis). Revue Med Interne. 2013;34:85-93.

13. Koizumi K, Haseyama Y, Machino R, Sato Y, Sawada K, Koike T. The hemophagocytic syndrome in prostate cancer revealed by disseminated carcinomatosis of the bone marrow. J Urol. 2002;168(3):1101-2.

14. Dumont L, Salaroli A, Lago LD, Thierry Gil T, Pepersack T. Prostate cancer and reactive haemophagocytic lymphohistiocytosis. Eur J Case Rep Intern Med. 2021;8(4):002425.