Histiocytic sarcoma (HS) is a rare malignancy encountered predominantly in men, usually starting at a median age of 51 years. The hematopoietic tumor originates from mature histiocytes produced in the bone marrow and presents mostly as a primary solitary tumor, affecting extranodal sites such as the bone marrow, skin, gastrointestinal tract, and lymph nodes (less common) [1].

To date, 25% reported that HS arises from low-grade B-cell lymphoma, which further trans-differentiate to HS [2]. Cases of HS manifesting as a secondary malignancy following chemotherapy therapy for other malignancies are also reported [3].

Diagnosis of HS is based on morpho-pathologic examination and immunohistochemistry staining with CD 163+, the high affinity scavenger receptor of the haptoglobin-hemoglobin complex and marker of macrophage lineage cells. CD 163+ immunohistochemistry staining has high sensitivity for neoplasms arising from histiocytes and therefore is crucial for establishing a diagnosis of HS [4].

HS has a bad prognosis and a high mortality rate due to its rarity and time consuming efforts until the diagnosis is made. There are few large cohort studies. Treatment options are limited and include surgical resection, adjuvant radiation, and chemotherapy [5].

**PATIENT DESCRIPTION**

A 34-year-old male refugee to Israel from Eritrea, with no significant medical history except appendectomy due to appendicitis (confirmed by pathology) in 2014, was admitted twice over a period of 6 months to our hospital with worsening of diffuse abdominal pain without any other symptoms. The patient denied weight loss or a family history of cancer.

At the first hospital visit the patient was evaluated in the emergency department by a surgeon. The physical examination and laboratory blood work were normal. Abdominal computed tomography (CT) scan revealed worsening of peritoneal and retroperitoneal lymphadenopathy compared to the previous scan from 2014, when an appendectomy was performed [Figure 1A].

The patient was admitted to the internal medicine ward with peritoneal and retroperitoneal lymphadenopathy for further investigations. Infectious investigations were negative for human immunodeficiency viruses, cytomegalovirus, Epstein-Barr virus, pulmonary tuberculosis, hepatitis B, hepatitis C, toxoplasma, clostridium, bartonella, salmonella, shigella, campylobacter, and three samples of stool for parasites. Bacterial genome sequences, Pan-PCR, were positive for propionibacterium. It was determined by infectious disease specialists that it was less likely Propionibacterium was responsible for our patient’s findings. CT guided retroperitoneal lymph node biopsy revealed histiocytic agglomer-
mm/Hg, pulse 100 beats per minute, regular, temperature 37.2°C. No jaundice or generalized lymphadenopathy was noted. Heart and lung examination was normal. Abdominal examination revealed generalized tenderness, without signs of rebound. Organomegaly was excluded. Blood examination showed new findings of bicytopenia, with a normocytic normochromic anemia, hemoglobin 5.7 g/dl and a platelet count 11,000 mm3. Lactate dehydrogenase was within normal range 511 U/L. Imaging included a chest X-ray that showed no pleural effusion or consolidation and an abdominal X-ray with no signs of intestinal obstruction. The abdominal CT scan revealed new bilateral pleural effusions and moderate ascites in addition to further enlargement of peritoneal, retroperitoneal, mesenteric, and pelvic lymphadenopathy compared to previous abdominal CT performed 3 months before [Figure 1B, 1C].

Further investigation included a bone marrow biopsy, which demonstrated prominent infiltrations of large foamy and granular histiocytes that compromised 45–50% of total bone marrow cells. A primary suspicion of a chronic infection etiology such as tuberculosis, leprosy, or brucellosis was considered. No sign of malignancy was observed.

After numerous biopsy results from several lymph nodes, duodenum, and bone marrow without reaching a clear diagnosis, it was decided that a diagnostic laparotomy was necessary. During surgery, three peritoneal lymph nodes, sized 2–3 cm, were excised. The pathology report revealed strong CD68+ staining for histiocytes compatible with a malignant configuration of histiocytes. Finally, a diagnosis of nodal histiocytic sarcoma with bone marrow involvement was revealed. The diagnosis was confirmed with the specific CD163+ stain. The patient was transferred to the hematology-oncology department for further treatment. Treatment options included NHL chemotherapy regimens-cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); ifosfamide, carboplatin, and etoposide (ICE); and adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD)l and thalidomide.

The patient started treatment with two CHOP cycles during 1 month, followed by three consecutive days of intravenous treatment with etoposide and ifosfamide. After treatment, a follow-up abdominal CT scan was performed, which revealed regression of bilateral pleural effusion, ascites, and central abdominal lymphadenopathy [Figure 1D]. No regression of mesenteric and peritoneal lymphadenopathy was observed. Chemotherapy treatment was changed and the patient received three days of ICE regimen and then continued with oral thalidomide. After 5 weeks of treatment, an abdominal CT scan was performed and showed unremarkable changes. Due to chemotherapy treatment failure, the patient continued with conservative measures.
The first biopsy, which was performed on June 2017, was a CT guided core needle biopsy from a retroperitoneal lymph node showed a lymphohistiocytic infiltrate that was not diagnostic.

This biopsy was followed by a trephine bone marrow biopsy on December 2017. It revealed a hypercellular bone marrow, cellularity approaching 95%, containing all hematopoietic cell lines reaching maturation admixed with large histiocytes containing voluminous foamy cytoplasm [Figure 1A, 1B].

These cells, which occupied about 40–50% of the cellular population, were positive for CD68+ and negative for S-100 protein and CD1a+. PAS and Ziehl Neelsen stains were negative for microorganisms. Very rare scattered enlarged cells, highlighted by an arrow in Figure 1A and Figure 1B, were also seen, the nature of which was not completely clear at that time. The possibility of activated macrophages was entertained. This biopsy was given a generic diagnosis of an infectious/inflammatory condition.

The third diagnostic biopsy, conducted in January 2018, was an excisional specimen of a peritoneal lymph node by laparotomy. Although foci of foamy histiocytes were seen they were alternating with larger areas containing sheets of pleomorphic malignant cells demonstrating large nuclei with vesicular chromatin, prominent nucleoli and ample pinkish cytoplasm. At other foci the tumoral cells assumed a spindle cell morphology and were arranged in storiform pattern. The cells were arranged in sheets occupying the lymph node parenchyma and also infiltrated the sinusoids, causing them distension.

Multinucleated malignant cells were readily observed [Figure 1C]. The neoplastic cells were positive for the monocytic/histiocytic lineage markers including CD68+ (clone: PG-M1) [Figure 1D], CD11c+ and the most specific monocytic/histiocytic marker CD163+ also demonstrated intra-sinusoidal growth pattern. CD4+ was also positive while CD33+ and HLA-DR immunostains were focally positive. The diagnosis of HS was established.

Our patient had an unusually long course of disease that lasted for 3 years. After one year of recurrent hospitalizations, 7 months of mixed chemotherapy regimens with CHOP, ICE, ABVD, and thalidomide with lack of remission, the patient died in the hemato-oncology department due to his advanced disease.

**References**