Histiocytic Sarcoma

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ABSTRACT Histiocytic sarcoma is a rare hematopoietic malignancy originating from the monocyte/macrophage bone marrow lineage. HS can occur in isolation or in association with other hematological neoplasms such as non-Hodgkin's lymphoma, myelodysplasia, or acute leukemia. Clinically, HS can affect lymph nodes, gastrointestinal tract, skin, bone marrow, and spleen as well as the central nervous system. Most cases of HS follow an aggressive clinical course, with most patients dying of progressive disease within one year of diagnosis.

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KEY WORDS: bone marrow, histiocytic sarcoma, immuno-histochemistry, bad prognosis, lymphadenopathy

The exact incidence of histiocytic sarcoma (HS) in adults is unclear. Clinical data are mostly limited to case series [1]. The development of immuno-histochemistry (IHC) has helped to differentiate HS from large cell lymphomas of B or T cell type. Diagnosis is only possible by histopathology and confirmed by immuno-reactivity of the neoplastic cells for specific markers: CD163+, CD68+, lysozyme, and CD4 [2-4] [Figure 1].

CD163+ is a sensitive and apparently restricted marker for identifying malignancy of histiocytic origin and is, therefore, crucial in the diagnosis of histiocytic sarcoma

CD163+, a hemoglobin scavenger receptor, is a specific marker of histiocytic lineage and used as a significant diagnostic tool for evaluating HS [3,5] while excluding other differential diagnosis such as other histiocytic/dendritic cell neoplasms, myeloid neoplasms, lymphomas, melanoma, and carcinoma [6,7] [Figure 1].

HS is a disease of exclusion. HS can affect solitary organs such as lymph nodes, skin, bone marrow, and. spleen. It can affect the central nervous system and gastrointestinal tract. It is defined as primary HS. To date, less than 20% of the cases reported are considered as primary [8]. Symptoms are related to local compression of surrounding organs or express with constitutional manifestations such as fever or weight loss. Due to the rarity of lymph node manifestation (less than 1% [9]) most studies were conducted on extranodal HS and were based on cohorts of 5 and 14 patients [3,10]. When the main manifestation is with lymphadenopathy, a differential diagnostic with lympho-proliferative diseases is needed. This diagnostic tool, including secondary to autoimmune diseases such as Sjögren's syndrome and IgG4 related disease, is warranted [11,12]. In our case both differential diagnostics were excluded by IHC.

A finding of histiocytosis should lead to an investigation to exclude an underlying malignancy

HS has been associated with a number of hematological malignancies, emerging years after the first remission. It is defined as secondary HS. The risk factors are unknown. One theory suggests histiocytic lesions share the same cytogenetic features with the original leukemia or lymphoma. It could only be speculated that an immuno-phenotypical evolution and/or the effect of chemotherapy could play a role [13,14].

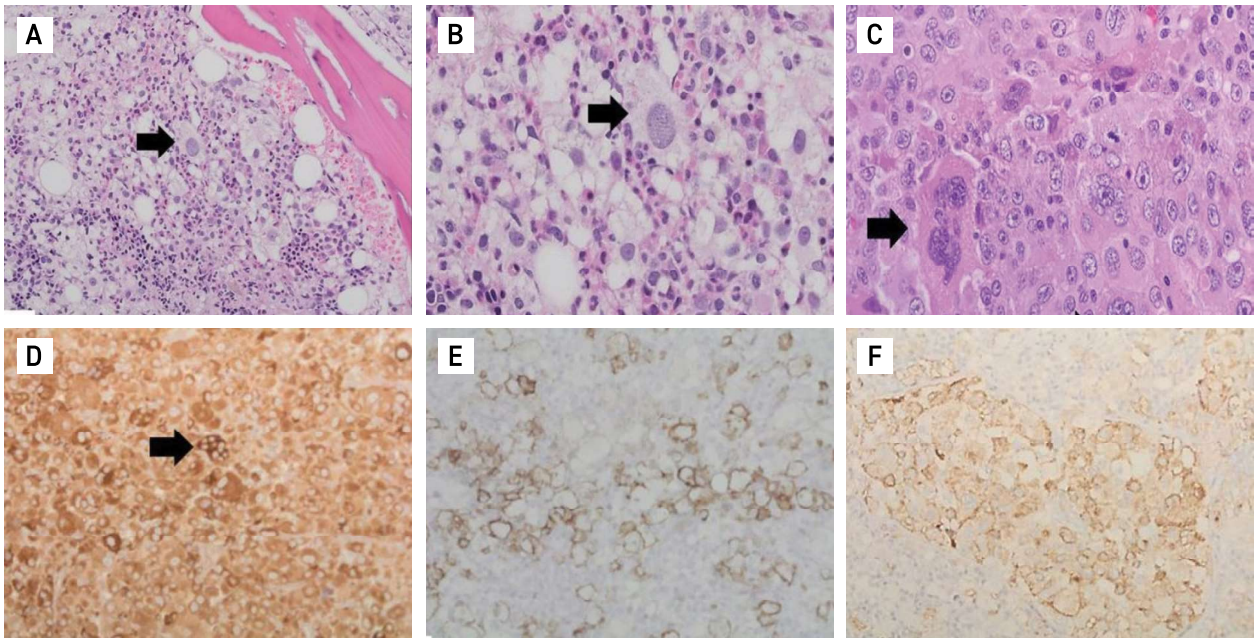
In one study based on a cohort of 23 patients, the outcome of de novo HS (17 patients) was better than secondary HS (6 patients) with higher survival rates. It was also noted that secondary HS had an aggressive course of disease compared to de novo HS [15].

A study from 2017, which included 87 patients with HS and dendritic cell neoplasms, used three prognostic parameters to classify and compare patients with HS (50 patients) and patients with non HS tumors (37 patients). The prognostic parameters were represented by high LDH, the lymphoma staging system (Ann Arbor) and performance status developed by the Eastern Cooperative Oncology Group. The study showed that patients with HS had a lower survival rate compared to patient with non HS tumors. It was also noted that prognosis and survival were substantially lower in patients with three prognostic factors compared to patient with no prognostic factors [8].

To date, a standard treatment for HS does not exist, due to the rarity of the disease. Treatments with various ranges of success are based on data from few case reports and case series that use lymphoma protocols. Treatment options for localized disease include: surgical resection, adjuvant radiation and chemotherapy [9,16].

Treatment options for systemic disease include: allogeneic hematopoietic stem cell transplantation (alloSCT) and auton-

Figure 1. Histologic images from the bone marrow biopsy and peritoneal lymph node excision
[A] Bone trabecula on the right and adjacent hypercellular bone marrow (cellularity approaching 95%) containing all three hematopoietic cell lines. Notice multiple foamy histiocytes and an enlarged atypical cell (black arrow); H&E stain × 100; **[B]** Magnification of the bone marrow biopsy at the site of the enlarged atypical cell (black arrow). Notice the multiple foamy histiocytes surrounding this cell admixed with granulocytes and plasma cells in addition to an erythroid island (left lower corner); H&E stain × 400. **[C]** Peritoneal lymph node excision demonstrating sheets of large pleomorphic cells with large nuclei, open chromatin, prominent nucleoli and abundant pinkish cytoplasm. Malignant multinucleated giant cells (black arrows) were readily identified; H&E stain × 400. **[D]** CD68+ (clone: PG-M1) immunostain reveals strong and diffuse cytoplasmic staining in the tumoral cells including the multinucleated malignant cells (black arrow); IHC × 100. **[E,F]** Membrane staining for CD11c+ and the most specific histiocytic marker CD163+ respectively. In panel F, the malignant histiocytes are located within an expanded sinus. A typical tumor cell localization in this tumor, IHC × 200



omous SCT. Few single-case reports with favorable outcomes were reported [17]. In one study thalidomide treatment was successful in stabilizing HS progression in two patients after allo-SCT [18]. Other studies showed that a subset of patients with HS harbor BRAF V600E mutations. Favorable responses to kinase inhibitors, vemurafenib, and trametinib were documented [19,20].

Recent reports have demonstrated a high rate of PD-L1 expression in histiocytic disorders, suggesting a potential therapeutic target. Nivolumab treatment was successful in one patient [21].

DISCUSSION

The finding of histiocytosis demands an investigation in order to exclude an underlying malignancy. Extreme measures such as performing a laparotomy with removal of entire lymph nodes could be essential and mandatory [22]. The clinical course of HS is frequently aggressive with an associated high mortality rate; stage of disease and possibly tumor size appear to have a prognostic significance.

CONCLUSIONS

CD163+ is a sensitive and apparently restricted marker for identifying malignancy of histiocytic origin and is, therefore, crucial in the diagnosis of HS. To date, no optimal or standardized treatment regimen is available for HS, regimens are borrowed from lymphoma protocols and HS patients have a bad prognosis.

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It is not what we do, but also what we do not do, for which we are accountable.

Jean-Baptiste Poquelin, known by his stage name Molière,, actor and playwright (1622–1673), French playwright, actor, and poet

Capsule

Change in the incidence of stillbirth and preterm delivery during the COVID-19 pandemic

High rates of preterm birth and cesarean delivery have been reported in women with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. However, studies have inadequate power to assess uncommon outcomes like stillbirth (fetal death ≥ 24 weeks gestation). **Khalil** and co-authors assessed the change in stillbirth and preterm delivery rates during the pandemic. There were 1681 births (1631 singleton, 22 twin, and 2 triplet pregnancies) in the prepandemic period and 1718 births (1666 singleton and 26 twin pregnancies) in the pandemic period. There were fewer nulliparous women (45.6% vs. 52.2%; $P < 0.001$) in the pandemic period than in the prepandemic period and fewer women with hypertension (3.7% vs. 5.7%; $P = 0.005$) in the pandemic period than the prepandemic period, and there were no significant differences in other maternal characteristics. The incidence of stillbirth was significantly higher during the pandemic period (n=16, 9.31 per 1000 births; none associated with COVID-19) than during the prepandemic period (n=4, 2.38 per 1000 births, difference 6.93, 95%CI, 1.83–12.0, per 1000 births; $P = 0.01$), and the incidence of stillbirth was significantly higher when late terminations for fetal abnormality were excluded during the pandemic period (6.98 per 1000 births vs. 1.19 per 1000 births in the prepandemic period; difference 5.79, 95%CI, 1.54–10.1; $P = 0.01$). There were no significant differences over time in births before 37 weeks gestation, births after 34 weeks gestation, neonatal unit admission, or cesarean delivery. During the pandemic period, 19 patients with COVID-19 were hospitalized in the study site maternity department. None of the pregnant women who experienced stillbirth had symptoms suggestive of COVID-19, nor did the postmortem or placental examinations suggest SARS-CoV-2 infection. Universal testing for SARS-CoV-2 started on 28 May 2020, and only one pregnant woman, who had a live birth, had a positive test result.

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