Case Series

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Pathology Section

Cutaneous and Nodal Histiocytic Sarcoma: A Series of Five Cases

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ABSTRACT

Histiocytic Sarcoma (HS) is an extremely rare haematolymphoid neoplasm that exhibits morphological and immunophenotypic features indicative of histiocytic differentiation. In most cases, it is misdiagnosed as Diffuse Large B-Cell Lymphoma (DLBCL) or anaplastic large cell lymphoma. HS is a diagnosis of exclusion, necessitating extensive immunophenotypic analysis to finalise the diagnosis. Hereby, authors present a case series of five cases diagnosed as HS based on histomorphology and an extensive Immunohistochemistry (IHC) panel. A total of five cases reported as HS over a five-year period (2018 to 2023) were diagnosed at the Department of Pathology. All demographic and clinical data, as well as treatment history, were collected from the patients and their family members. Paraffin-embedded blocks were retrieved from the archive, and routine Haematoxylin and Eosin (H&E) and special stains like Periodic Acid-Schiff (PAS) were performed. Microscopy revealed sheets of round to oval tumour cells with small round nuclei, inconspicuous nucleoli, and moderately microvacuolated cytoplasm. An extended IHC panel was applied to confirm the microscopic findings. All five cases exhibited intense immunoreactivity for Leukocyte Common Antigen (LCA) and showed strong positivity for the histiocytic marker CD68, while CD163 demonstrated variable cytoplasmic positivity. Dako R antibody at a dilution of 1:100 was used for the IHC analysis. This case series aims to highlight the importance of clinical, radiological, histological, and immunohistochemical properties of this rare neoplasm for early diagnosis and proper management.

Keywords: Haematolymphoid neoplasm, Histiocytes, Malignant histiocytosis

INTRODUCTION

The HS is a rare haematolymphoid malignant neoplasm of unknown aetiology, displaying features of histiocytic differentiation both morphologically and immunophenotypically [1]. A large number of cases have been misdiagnosed as DLBCL and anaplastic large cell lymphoma. Since HS is always a diagnosis of exclusion, extensive immunophenotypic analysis is required to rule out those conditions that may be misdiagnosed as HS. The US National Cancer Institute's SEER program conducted the largest population study to date, which included 159 cohorts and collected incidence and survival data on HS between 2000 and 2014. After a follow-up period of 7.5 months, 66 out of the 159 patients died-24 due to HS and 42 due to other co-existing malignancies. The overall incidence was found to be 0.017 per 1,000,000 individuals [2]. The incidence in the Indian population is unknown. Generally, the involved sites are the skin and connective tissue, followed by lymph nodes, the intestinal tract, respiratory systems, and the nervous system. A slight male dominance was observed, with an age range from infancy to older age, but it is most common in adults [1,2].

A small number of cases have been reported in conjunction with germ cell tumours, Non Hodgkin's Lymphoma (mostly follicular), Chronic Lymphocytic leukaemia (CLL)/Small Lymphocytic Lymphoma (SLL), and Myelodysplastic Syndromes (MDS); however, most cases present as isolated occurrences [3]. The diagnosis of HS is predominantly based on the confirmation of histiocytic lineage and the exclusion of other large cell malignancies, such as lymphoma, carcinoma, and melanoma, through the use of an extensive immunophenotypic panel [4]. For confirmation, at least one of the histiocytic differentiation markers-either CD68, CD163, or lysozyme-should show positivity, along with the absence of Langerhans cell markers (CD1a), myeloid cell markers (MPO, CD13), and follicular dendritic cell markers (CD21, CD35) [1].

HS is generally an aggressive neoplasm that is diagnosed at late stages (III/IV) and shows a poor response to conventional treatment protocols [1]. A large number of patients die due to late clinical stage presentation and higher disease burden. The median Overall Survival (OS) for HS alone is approximately 16 months, which is even shorter when associated with concomitant malignancies [2]. Exceptions exist for localised and small primary lesions, where early detection of the disease leads to better long-term survival outcomes. The purpose of presenting the current case series is to comprehend the clinical course, diagnostic challenges in early detection, and prognostic variables of this rare neoplasm in the Indian context.

CASE SERIES

A total of five cases diagnosed as HS were reported within a duration of approximately five years (October 2018 to December 2023) at the Department of Pathology in a tertiary care centre in northern India. Cases were included based on morphology and confirmation by at least one immunophenotypic histiocytic differentiation marker (CD68 or CD163). Cases that were negative for LCA and immunoreactive for any other differentiation markers, such as epithelial (CK), melanocytic (HMB45, MELAN A), myeloid (CD13, MPO), and immaturity markers for leukaemia (CD34, TdT), were excluded from the study. Available clinical data included presenting symptoms, site and size of the tumour, tumour progression, distant metastasis, history of chemotherapy, and disease-free survival [Table/Fig-1]. Four out of the five diagnosed cases were male, resulting in a male-to-female ratio of 4:1, with ages ranging from 18 to 55 years (mean age approximately 32 years). An extensive IHC panel of markers for each case has been tabulated in [Table/Fig-2].

Case 1

A 21-year-old female presented with a lump on her left lateral malleolus. Contrast-Enhanced Magnetic Resonance Imaging (CE-MRI) revealed an ill-defined, heterogeneous enhancing area with postcontrast enhancement at the anterior aspect of the ankle and foot, along with a small pocket of collection. Signal alteration was noted in the cuboid bone [Table/Fig-3a]. Grossly, the tumour measured 3.5×3.0×2.5 cm and was greyish-white, firm to hard in

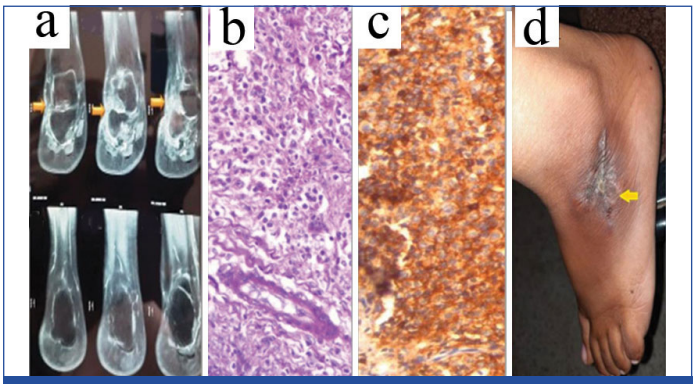
Case no.	Age (years)/Sex	Site	Size (cm)	Presenting symptoms	Progression	Distant metastasis	Chemo-therapy	Survival
1	21/F	Left lateral malleolus	4.0x3.6x1.7	Swelling, induration	Indolent	No	No	Disease free after 22 months since diagnosis
2	18/M	Left leg	12x7x6	Swelling, induration, pain, discharge	Aggressive	Multiple cutaneous*, Cervical lymphadenopathy	Yes	Died 20 days after two cycles of chemotherapy
3	55/M	Right forearm	4.8×4.5×5.0	Swelling, pain, unable to move wrist joint	Locally aggressive	No	No	Disease free after one month of diagnosis
4	21/M	Right arm	3.0x2.5x1.6	Swelling, painless	Aggressive	Yes	Yes	Died after three months of diagnosis
5	45/M	Left cervical lymph node	2.5x2.0x1.8	Cervical lymphadenopathy	Indolent	No	No	Disease free after five years of diagnosis

[Table/Fig-1]: Clinical and demographic characteristics.
*Sample was received from metastatic abdominal swelling

IHC markers	Case 1	Case 2	Case 3	Case 4	Case 5
LCA	Intense+	Intense+	Intense+	Intense+	Intense+
CD-68	Intense+	Intense+	Intense+	Intense+	Intense+
CD-163	Intense+	Intense+	-	-	Moderately+
S100	Focal weak+	-	Focal weak+	-	Focal weak+
CK	Negative	Negative	Negative	Negative	-
CD-34	Negative	Negative	Negative	Negative	Negative
MPO	Negative	Negative	Negative	Negative	Negative
CD3	Positive in T cells	-	Negative	-	-
CD1a	Negative	Negative	Negative	Negative	-
HMB-45	Negative	Negative	Negative	Negative	Negative
Vimentin	Positive	Positive	Positive	Positive	Positive
Ki67	5%	80%	10%	30%	5%

[Table/Fig-2]: Extensive Immunohistochemistry (IHC) panel.
LCA: Leukocyte common antigen; CD: Cluster of differentiation; CK: Cytokeratins; MPO: Myeloperoxidase; HMB: Human melanoma black

consistency, with focal areas of haemorrhage noted. Microscopy showed sheets of round to oval, medium-sized tumour cells with small round nuclei, irregular nuclear outlines, inconspicuous nucleoli, and moderately microvacuolated cytoplasm. These tumour cells were infiltrating the papillary dermis and adjacent connective tissue; however, the epidermis was free in cutaneous HS [Table/Fig-3b]. The differentials considered were lymphoma, malignant sarcoma, and malignant melanoma. Based on microscopy, the provisional diagnosis was low-grade sarcoma. The tumour cells exhibited intense membranous immunoreactivity for LCA [Table/Fig-3c], as well as intense cytoplasmic granular positivity for histiocytic markers CD68 and CD163. S100 showed focal weak positivity, while CK, CD34, MPO, and HMB45 were negative in the tumour cells. The Ki-67 index was approximately 5%. Surgical resection was performed, and the postoperative period was uneventful [Table/Fig-3d]. The patient was disease-free after 22 months of follow-up.

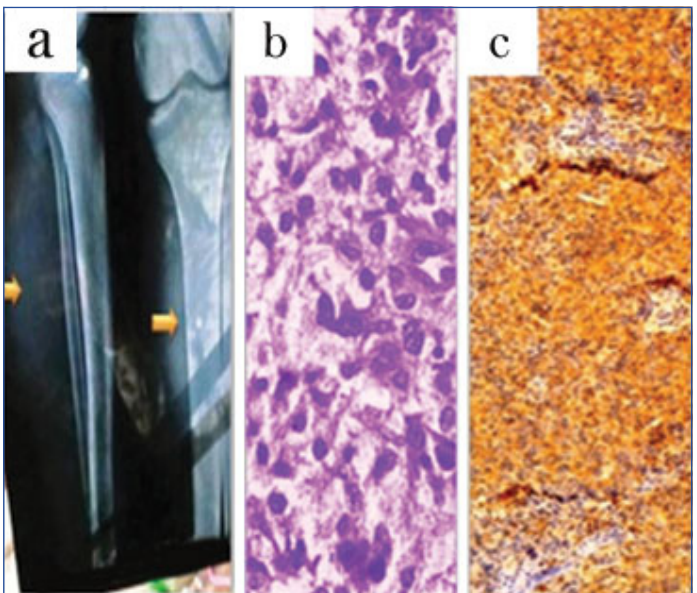


[Table/Fig-3]: a) An ill-defined heterogeneous enhancing area with postcontrast enhancement at anterior aspect of ankle and foot with small pocket of collection. Signal alteration was noted in cuboid bone (Case-1); b) Showing sheets of monomorphic cells having abundant clear cytoplasm. Bottom side show thick-walled blood vessel. (H&E, 200x) (Case-1); c) Immunohistochemistry (IHC) showing intense membranous positivity of LCA (Case-1); d) Postoperative picture of swelling below left malleolus (Case-1).

Case 2

An 18-year-old male presented with a chief complaint of swelling associated with on-and-off dull aching pain in the left leg over the past six months, followed by multiple abdominal swellings and cervical lymphadenopathy in the last 1.5 months. An X-ray revealed an ill-defined soft-tissue mass measuring approximately 12×7×6 cm in the left leg without underlying bony involvement [Table/Fig-4a]. A suspected metastatic abdominal lump was sent to the facility for evaluation.

Gross examination of the lesion revealed it to measure 3.3×3.0×2.0 cm, exhibiting a greyish-brown colour and a firm to hard consistency, along with large areas of necrosis. Microscopic examination of the abdominal swelling showed round to oval bizarre cells with highly pleomorphic, hyperchromatic nuclei, irregular nuclear outlines, and moderate amount of cytoplasm [Table/Fig-4b]. Frequent atypical mitoses were observed, approximately 20 per 10 high power fields, along with significant tumour necrosis. Differential diagnosis considered included malignant high-grade sarcoma, malignant melanoma, lymphoma, and metastatic epithelial malignancy. The provisional diagnosis based on the microscopy findings was high-grade sarcoma. The tumour cells exhibited positivity for LCA, the histiocytic markers CD68 [Table/Fig-4c] and CD163, as well as vimentin, while being negative for CK, CD34, MPO, and HMB45. The Ki-67 index was approximately 80% in the hotspot. The patient received the Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (CHOP) regimen but unfortunately died after two cycles of induction chemotherapy due to suspected high tumour burden.

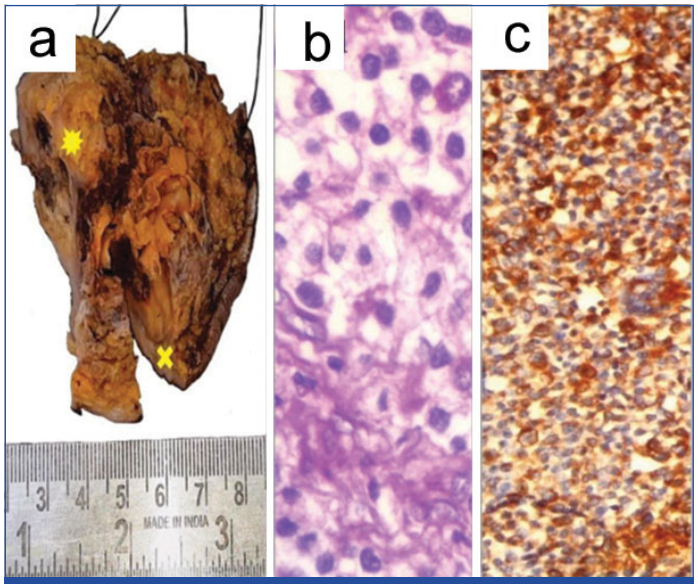


[Table/Fig-4]: a) On X-ray an ill-defined soft-tissue mass measuring ~12x 7x6 cm noted at left leg without underlying bony involvement (Case-2). b) High power (400x) microphotograph showing highly pleomorphic cells with irregular nuclear membrane, coarse chromatin, and moderate cytoplasm. (Case 2); c) Immunohistochemistry (IHC) showing intense cytoplasmic granular positivity of CD68 (Case-2).

Case 3

A 55-year-old male presented with swelling and infrequent low-grade pain associated with joint movement, as well as restricted movement in the right wrist joint over the past four months. A contrast-enhanced MRI (CE-MRI) revealed a well-defined solid cystic lesion measuring 4.8×4.5×5.0 cm on the ventral aspect of the right wrist joint. The lesion appeared hypointense on T1-weighted images and hyperintense on T2-weighted images. Gross examination of the lesion showed multiple septations and loculations [Table/Fig-5a]. The lesion measured 4.5×3.5×2.2 cm, was greyish-brown in colour, and had a rough and congested outer surface covered with skin. It was firm to hard in consistency.

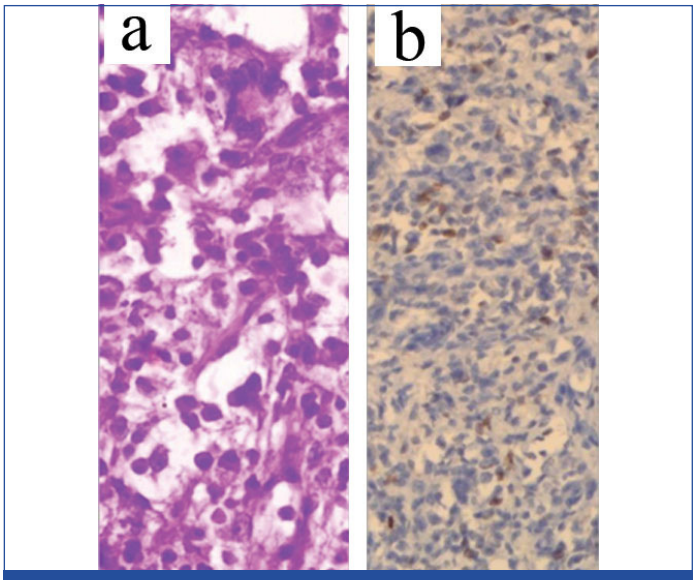
Microscopic examination revealed tumour cells with additional findings of occasional multinucleated giant cells and haemosiderin-laden macrophages. The deep resection margin was also positive [Table/Fig-5b]. The differential diagnosis considered included intermediate-grade sarcoma, melanocytic tumour, lymphoma, and malignant histiocytosis. The provisional diagnosis based on microscopy was a histiocytic lesion. The tumour cells showed positivity for LCA, the histiocytic marker CD68, and vimentin [Table/Fig-5c]. They were weakly positive for S100 and negative for CK, CD34, MPO, and HMB45. The Ki-67 index was approximately 10%. Surgical resection was performed, and the patient was doing well after one month of follow-up.



[Table/Fig-5]: a) Gross image of swelling left forearm of (Case-3). Astrix and cross show yellowish white solid areas; b) High power (400x) microphotograph showing monomorphic to polymorphic cells having abundant eosinophilic granular to clear to vacuolated cytoplasm and centrally placed nuclei. (Case 3); c) Immunohistochemistry (IHC) showing intense cytoplasmic positivity of vimentin (Case-3).

Case 4

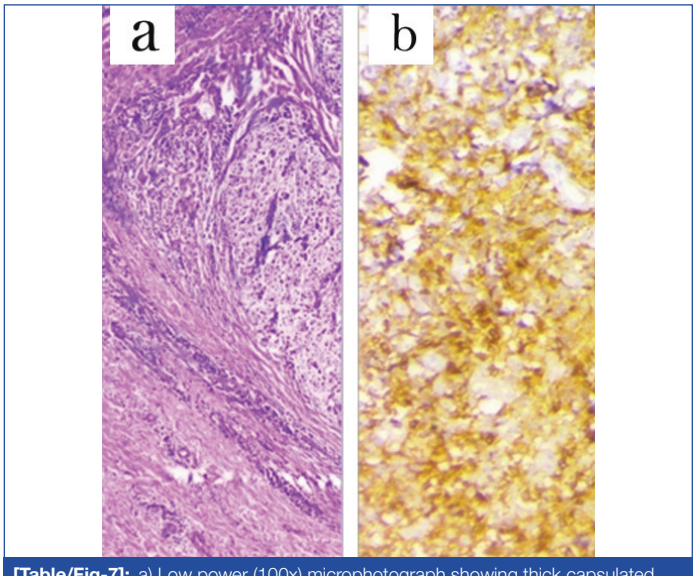
A 21-year-old male presented with a chief complaint of painless swelling in the right arm that had developed over the past 2.5 months. A CT scan revealed an ill-defined, locally infiltrative, heterogeneous enhancing soft-tissue lesion measuring approximately 3.0×2.5×1.5 cm. No obvious bony involvement was noted. Gross examination of the lesion showed it to be 2.8×2.5×2.0 cm, grayish-brown, and firm in consistency, with focal areas of old haemorrhage. Microscopic examination revealed findings consistent with the gross description, along with occasional multinucleated giant cells and haemosiderin-laden macrophages. The mitotic count was less than 5 per 10 high-power fields [Table/Fig-6a]. The differential diagnosis considered included intermediate-grade sarcoma, malignant histiocytic lesion, melanocytic tumour, and adnexal neoplasm. The provisional diagnosis was a malignant histiocytic lesion. The tumour cells were positive for LCA, the histiocytic marker CD68, and vimentin, while being negative for CK, CD34, MPO, and HMB-45. The Ki-67 proliferation index was approximately 30% [Table/Fig-6b]. The patient completed four cycles of induction chemotherapy using the CHOP regimen but unfortunately died three months after diagnosis.



[Table/Fig-6]: a) High power (400x) microphotograph showing sheets of monomorphic tumour cells. (Case 4); b) Immunohistochemistry (IHC) showing moderate nuclear positivity of ki-67 in ~ 30% cells (Case-4).

Case 5

A 45-year-old male presented with left cervical lymphadenopathy for one month. Clinically, the lymph node was a single firm mass, restricted in mobility, with unremarkable overlying skin, measuring approximately 2.5x2.0x1.8 cm. Grossly, the lesion measured 2.4×2.2×2.0 cm, showing a greyish-brown colouration, partially encapsulated, and firm in consistency, with no haemorrhage or necrosis. Microscopically, the lymph node was partially encapsulated with a thickened capsule. The nodal architecture was distorted due to the proliferation of neoplastic tumour cells of large size, characterised by eccentric nuclei with irregular nuclear outlines, vesicular chromatin, and abundant eosinophilic cytoplasm. Some cells also exhibited active phagocytosis [Table/Fig-7a]. The differential diagnosis considered were DLBCL, follicular lymphoma, histiocytic lesions, and melanocytic tumours. The provisional diagnosis was non-Hodgkin's lymphoma. These tumour cells were positive for LCA, as well as histiocytic markers CD68 and CD163 [Table/Fig-7b]. Surgical resection was performed, and the patient has been doing well five years postsurgical removal.



[Table/Fig-7]: a) Low power (100x) microphotograph showing thick capsulated node infiltrated by tumour cells intermixed with lymphocytes. Intervening septa are thick. (Case 5); b) Immunohistochemistry (IHC) showing moderate cytoplasmic positivity of CD163 (Case-5).

DISCUSSION

The HS is a rare neoplasm with limited reported case series. The disease is not restricted to a specific age group, as cases have been reported from infancy to old age; however, a few studies indicate that the most common affiliation is in adults [1]. In present case series, three showed cutaneous involvement, one had soft-tissue involvement, and one involved the lymph nodes.

Patra S et al., conducted a retrospective study of four cases of HS [3]. The radiological, microscopic, and IHC findings were consistent with those in of present study cases. The authors reported that two cases showed bone metastasis, and one of the patients received chemotherapy. In present series of five cases, only two showed distant metastasis, and two patients received chemotherapy. Susan Joy Philip D et al., described a series of four cases of HS, both visceral and cutaneous, with radiological and morphological findings similar to those in present cases [4]. All the cases exhibited intense staining for CD68 and CD163. Patients with multifocal disease received the CHOP regimen, and one patient also underwent radiation therapy. One patient died, while another remained disease-free after 12 years of follow-up.

Raj A et al., reported on a 70-year-old patient with multiple cutaneous and visceral gastrointestinal lesions diagnosed as HS based on microscopy and IHC. The Ki-67 index was 70% [5]. This case demonstrated an aggressive clinical course, similar to case 2 in present series, which also showed metastasis and a high Ki-67 index (~80%).

Various studies, such as those by Swerdlow SH et al., Jaffe ES and Chan JKC Wood GS et al., and Lauritzen AF et al., [1,6-8], have concluded that the diagnosis of HS is primarily based on histopathology, followed by IHC. The microscopic findings reveal a diffuse, dyscohesive proliferation of large, round to oval neoplastic cells. These tumour cells may be monomorphic or polymorphic, exhibiting abundant eosinophilic, granular, clear, or vacuolated cytoplasm, with centrally or eccentrically placed pleomorphic nuclei that have irregular, folded nuclear outlines and vesicular chromatin. In Case 2, there was marked pleomorphism, suggesting more aggressive behaviour [Table/Fig-4b]. Consistent findings in present study, as well as in various other studies [9], include malignant differentiation of histiocytes and destruction of the surrounding tissue. Other morphological differentials for HS include DLBCL, Langerhans cell sarcoma, anaplastic large cell lymphoma, metastatic carcinoma, and melanoma.

IHC is key to discriminating and narrowing down the differential diagnosis. CD-45 (LCA) is recommended and used in this series as a requirement to establish a lineage marker of haematopoietic origin [10,11]. All five cases showed intense membranous positivity for CD45. Histiocytes must express one or two histiocytic lineage markers, along with a typical absence of Langhans cells (CD1a), myeloid markers (CD13/CD33), and follicular dendritic markers (CD21) [1]. CD68 and CD163 are commonly expressed in most histiocytoses. CD68 is the earliest marker used to differentiate histiocytes, but it lacks specificity due to its expression in various other neoplasms, such as melanoma. Recent studies have considered CD163 to be a more specific histiocytic marker compared to CD63 [12,13]. In present study, all five cases showed intense cytoplasmic granular positivity for CD68, while three cases exhibited diffuse cytoplasmic positivity for CD163. A further IHC panel was applied to rule out other neoplasms. CD1a was used to rule out Langerhans cell tumour, MPO for myeloid neoplasms, and CD3 and CD20 to rule out T-cell and B-cell neoplasms a CK was negative to rule out any epithelial neoplasm. CD34 was applied to confirm that no blastic transformation had occurred [Table/Fig-2]. HMB-45 was negative to rule out any melanocytic tumour. The Ki-67 index was variable, ranging from 5 to 80%, signifying that histiocytoses may present with benign characteristics to poor aggressive behaviour.

No standard treatment regimen is available for histiocytoses; the current options include surgery with wide margins followed by chemotherapy and radiotherapy. The chemotherapy regimen is commonly similar to those given in DLBCL. CHOP with additional etoposide has shown promising results, with prolonged disease-free survival [14]. Histiocytoses are aggressive neoplasms that show poor responses to standard regimens. Tumour size and stage are the most important factors for prognosis [15]. Allogenic stem cell transplant is primarily reserved for relapsed cases, and complete response has been reported [16].

CONCLUSION(S)

The HS is a malignant, proliferative haematolymphoid neoplasm diagnosed by confirming histiocytic lineage and excluding other similar-looking neoplasms, such as carcinoma, lymphoma, melanoma, or sarcoma. The novelty of the current study was to understand the clinical, radiological, and histological spectrum of this rare malignancy. This study aims to highlight the importance of IHC in early diagnosis, as the lack of a standard regimen makes early detection a crucial step in the proper management of this aggressive disease.

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