

Primary Hodgkin's Lymphoma of the Sternum: Report of a Case and Review of the Literature

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ABSTRACT

Sternal masses present a unique diagnostic challenge in clinical practice. A wide array of differential diagnosis of a sternal mass includes osteomyelitis, tuberculosis, eosinophilic granuloma, sarcoma and lymphoma (usually Non-Hodgkin's) amongst others. Sternum is a rare site of Hodgkin's lymphoma and is usually misdiagnosed as tuberculosis or eosinophilic granuloma on routine histopathology. This delayed diagnosis culminates in death of patients. We report a 30-year-old lady who presented with swelling in upper part of chest wall since 1 month. Past history was significant for a similar swelling 2 years back, which was diagnosed as Hodgkin's lymphoma and treated with 4 cycles of chemotherapy at another centre (which led to resolution of the swelling). Examination revealed a 6x6.5cm firm swelling originating from the upper part of sternum. There was no lymphadenopathy or organomegaly. Histopathological examination (with immunohistochemistry) of the trucut biopsy from the swelling confirmed the diagnosis of Hodgkin's lymphoma (nodular sclerosis). Patient was diagnosed as a late relapse of primary sternal Hodgkin's lymphoma (stage IBE) and was administered 4 cycles of ABVD followed by local radiotherapy to the involved site which led to complete resolution of the disease as assessed by PET scan. We present this unusual case of primary sternal Hodgkin's lymphoma. Rarity of this entity, with diagnostic challenges encountered and treatment options available are highlighted in the current report. A pubmed search revealed 18 cases of sternal involvement in Hodgkin's lymphoma which have been tabulated.

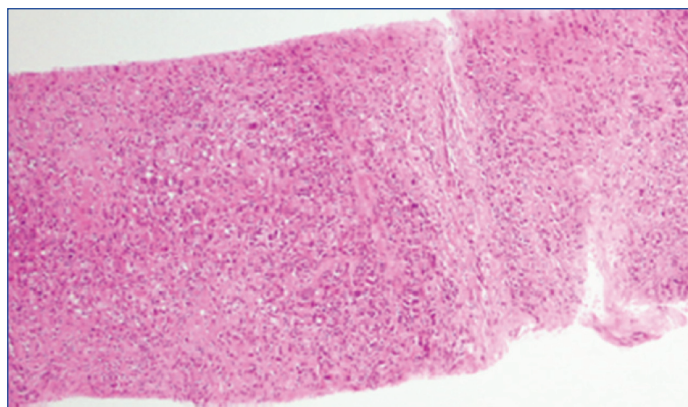
Keywords: Chemo-radiotherapy, Immunohistochemistry, Tuberculosis

CASE REPORT

A 30-year-old lady of Indian origin presented to our haematology clinic with complaints of swelling over the anterior chest wall of 1 month duration, associated with low grade fever (100°F) and significant weight loss (5kg over 1 month). She denied swelling in any other part of body, night sweats, cough or evening rise of temperature. Past history was significant for a similar swelling 2 years back which was diagnosed at a different centre as Hodgkin's lymphoma (nodular sclerosis) after an open biopsy from the upper part of sternum. Patient was administered chemotherapy every 15 days, for a total of 8 courses (or 4 cycles, 2 courses per cycle). Records of staging and details of chemotherapy regimen were not available. No local radiotherapy was administered after chemotherapy. Swelling subsided following 4 cycles of chemotherapy and patient remained asymptomatic till the current presentation. She didn't report back to the initial treatment centre in between.

On examination, the blood pressure was 120/76 mmHg and pulse was 74/minutes. General examination was not remarkable and there was no palpable lymphadenopathy. Chest examination revealed a midline swelling of approximately 6x 6.5cm in size originating from the upper part of the sternum. On palpation, swelling was fixed, firm and non-tender with smooth margins without any overlying erythema or fistula. An old surgical scar mark of 3cm (from previous open biopsy) was visible. Per abdomen examination revealed no organomegaly and rest of the systemic examination was unremarkable. Patient's blood test's were as follows - Hb-100gm/L, white cell count- $12 \times 10^9/L$, differential counts- 70% neutrophils, 25% lymphocytes, 5% eosinophils, platelet count- $350 \times 10^9/L$, ESR -20mm/hour and LDH - 250U/L.

Trucut biopsy from the swelling revealed fibrous bands with lacunar variant of Reed Sternberg cells in a background of polymorphs, lymphocytes, eosinophils and plasma cells, a picture consistent with nodular Sclerosis Hodgkin's lymphoma [Table/Fig-1]. On immunohistochemistry, the atypical Reed Sternberg cells were

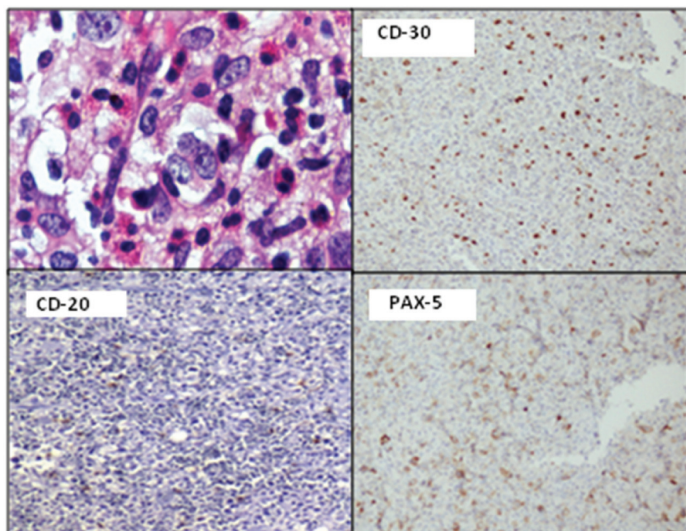


[Table/Fig-1]: Low magnification view (X 100, Haematoxylin and eosin) of the sternal biopsy showing lymphoid aggregates (consisting of atypical Reed Sternberg cells and a reactive background) separated by fibrous bands.

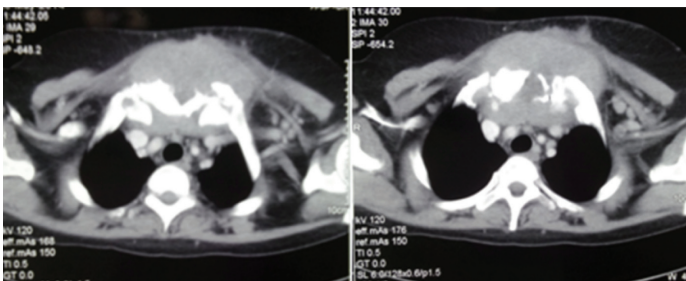
positive for CD-15, CD-30 and PAX-5 and negative for CD-45, ALK, BCL-2 and CD-20, a pattern typical of classical Hodgkin's lymphoma [Table/Fig-2].

Contrast Enhanced CT scan (CECT) of chest, abdomen and pelvis revealed a large lobulated heterogeneously enhancing soft tissue mass measuring about 8x8cm in size involving the sternum, causing its destruction and extending into the anterior mediastinum with encasement of the left brachiocephalic vein [Table/Fig-3]. There was no mediastinal or abdominal lymphadenopathy and hepato-splenomegaly. Bone marrow examination was normal. Patient was diagnosed as a case of late relapse of nodular sclerosis Hodgkin's lymphoma (Ann Arbor stage IBE). Australia antigen, Hepatitis C serology and HIV-1 and 2 were negative. Baseline 2D-echocardiogram revealed an ejection fraction (EF) of 60%. Pulmonary function test was normal.

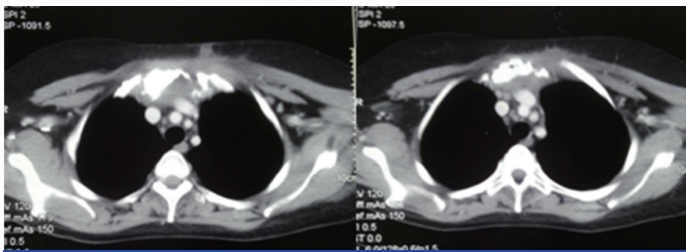
In view of late relapse and a localized disease, patient was planned for 4 cycles of ABVD followed by Involved Field Radiotherapy (IFRT) to the residual mass. After an informed and written consent, she



[Table/Fig-2]: High power magnification (x400, Haematoxylin and eosin) of the sternal biopsy showing characteristic Reed Sternberg cells (upper left). Immunohistochemistry of these atypical cells reveals positivity for CD-30 (upper right), PAX-5 (lower right) and negativity for CD-20 (lower left).



[Table/Fig-3]: Contrast enhanced CT (CECT) chest of the patient showing a lobulated heterogeneously enhancing soft tissue mass involving the sternum and extending into anterior mediastinum causing destruction of the sternum.



[Table/Fig-4]: CECT chest of the same patient showing a significant reduction in the size of the lesion after 4 cycles of ABVD regimen with a small residual fibrotic mass.

was administered 4 cycles of ABVD regimen (Adriamycin-25mg/m², Bleomycin-10U/m², Vinblastine-6mg/m² and Dacarbazine-375mg/m² q2 weekly every 28 days) followed by IFRT (30 Gy over 18 fractions) to the local site .

Patient's swelling subsided after 4 cycles of chemotherapy. Repeat CECT chest done at the end of treatment revealed 95% reduction in the size of the mass lesion. However, a small residual mass was detected in the anterior mediastinum abutting the left brachiocephalic vein [Table/Fig-4]. FDG PET-CT further characterized the residual mass as sclerotic on the basis of its faint FDG avidity. Patient achieved complete remission after therapy and is in our regular follow-up since 1 year without any recurrence of sternal swelling or any clinically palpable lymphadenopathy.

DISCUSSION

Hodgkin's lymphoma (HL) is a nodal B-cell neoplasm which characteristically presents as painless cervical lymphadenopathy. Extranodal presentation of HL is rare in an immunocompetent patient. Most commonly involved sites are gastrointestinal tract, pulmonary system, thyroid, skin, genitourinary tract and central

nervous system [1]. Skeleton constitutes an unusual extranodal site in HL. Bone involvement is a feature of advanced HL and occurs in about 10-20% cases at some time during the course of disease (30-50% at the time of autopsy) [2]. Osseous HL at initial presentation is extremely rare (1-4%) [3]. Although thought to be only osseous at initial presentation, such cases are generally found to have non-osseous involvement as well during evaluation. Therefore, true 'primary' osseous HL is an exception [2]. Primary osseous HL therefore represents a distinct and extremely rare subset of cases whereby bone is the only site of involvement. Primary bone lymphoma is defined as being limited to bone with or without associated soft tissue component and no regional lymphadenopathy at diagnosis and for 6 months of follow-up. In a study of 442 cases of primary bone lymphomas, HL represented only 13 such cases [4]. It is important to remember that 'bone marrow' involvement which occurs in 5-10% of HL patients is not synonymous with 'primary osseous HL' [2]. Bone marrow involvement is classified as stage IV HL whereas 'primary solitary osseous HL' is stage IE according to Ann Arbor staging [1]. Bone involvement in HL may be due to primary growth into bone or secondary to haematogenous spread or involvement by an adjacent lymph node mass [5]. In case of osseous HL due to an adjacent lymph nodal invasion, suffix 'E' is added to the staging. However, if bone is involved due to advanced systemic disease, patient is classified as stage IV [6]. Osseous HL therefore, is of four subtypes: 1) Primary solitary HL; 2) primary multifocal HL; 3) osseous and non-osseous HL; and 4) osseous HL at recurrence [1]. Spine (thoracolumbar), pelvis, ribs, femur, sternum, clavicle and skull are the most commonly involved skeletal sites in HL (in descending order) [5]. Sternal involvement in HL is distinctly uncommon and has not been reviewed separately in the literature. Out of all the reported cases of osseous HL in the English literature, we selectively reviewed the data of 'sternal HL' [Table/Fig-5] [2,3,5-17].

After an extensive search at PUBMED using the MESH terms 'Hodgkin's, sternum and osseous', we could identify 18 cases of HL with sternal involvement (both primary and secondary, both initial presentation and at relapse) in the English literature from 1966-2015. Along with sternal involvement, 10 patients had an additional lymph node involvement, 5 had involvement of other skeletal sites and only 3 patients had isolated or 'primary' sternal involvement. Male were more commonly affected than females (M: F-2:1) and median age was 27.7 years (7-82 years). Three cases of paediatric sternal Hodgkin's lymphoma (case no.2, 5 and 14) were also identified. Histology was available in 10 cases for review. Amongst the available histological subtypes, nodular sclerosis was the most common subtype (80%) followed by mixed cellularity (20%). Seven cases (38.8%) were initially misdiagnosed (most commonly as tuberculosis and eosinophilic granuloma) based on histopathological examination. Eighty eight (88%) percent of the cases had sternum involvement at initial presentation and an additional 12% had it at relapse. Treatment included Radiotherapy (RT) alone in 7 (38.8%), combined chemo-radiotherapy in 6 (33.3%), chemotherapy alone in 3 (16.6%), Auto SCT in 1 (5.5%) patient. One patient couldn't receive treatment due to poor performance status. Outcomes of 17 cases indicates that 10 (59%) were alive and 7 (41%) died of the disease.

Only 3 patients out of 18 (17%) had a 'primary sternal' Hodgkin's lymphoma. All 3 were males (mean age-35 years). Two of them had sternal involvement at initial presentation (treated by only RT and died) and one had it at relapse (treated by high dose chemotherapy followed by Auto SCT). Therefore, we summarize that isolated sternal involvement in HL is extremely rare and usually involves males in their third decade. Radiotherapy alone might not be an optimal therapy in these cases as evidenced by a high mortality rate (100%) in cases receiving it. Our case is the first reported case where sternum was the only site of Hodgkin's disease both

S.No	Author	year	age	sex	sternal involvement-primary/relapse	initial diagnosis	sternal involvement at initial diagnosis	treatment given for initial diagnosis	site of involvement along with sternal mass	stage	subtype	treatment given	Outcome
1	Arnold et al., [7]	1966	21	F	primary	Chondrosarcoma	Y	resection of the sternal mass	Sternum (15x15 cm) and mammary nodes	NA	NA	resection followed by post-operative RT	Alive at 24 months
2	Manoli et al., [8]	1986	14	M	primary	eosinophilic granuloma	Y	-	Sternum only	NA	NA	RT only due to incorrect diagnosis of eosinophilic granuloma	Died
3			19	F	primary	HL	Y	-	Sternum (3x4 cm) and bilateral supraclavicular lymphadenopathy	IIAE	NS	4000 rads mantle field and peri-aortic RT with 1000 rads boost to the sternum	Alive at 3 years after presentation
4	Sullivan et al., [6]	1987	22	F	primary	HL	Y	-	Sternum (6 cm) with axillary LN	NA	NS	Mantle cell RT	Alive
5	Miano et al., [9]	1990	9	M	primary	HL	Y	-	Sternum (4 cm), inguinal LN	IIIAE	NS	6XMOPP/ABVD followed by RT	Alive at 32 months
6	Borg et al., [10]	1993	23	M	NA	HL	NA	NA	Thoracic spine, pelvis, femur, sternum, skull	IIA	NS	Chemo + radiotherapy	Died
7	Ostrowski et al., [2]	1998	50	M	primary	HL	Y	-	Sternum and bilateral axillary LN	NA	NA	RT	Died
8			58	M	primary	HL	Yy	-	Anterior chest wall soft tissue	NA	NA	RT	Died
9			20	M	Relapse	HL	N	NA	Sternum and clavicle	NA	NA	RT	Died
10	Karimi et al., [11]	2001	82	F	primary	HL	Y	-	Two masses outside chest wall, one at middle of thoracic inlet, another at right side of sternum (5x5cm)	NA	NA	no treatment received due to poor PS	died 2 weeks after diagnosis
11	Petkov et al., [12]	2006	33	M	Relapse	HL	N	6xCOPP/ABV followed by RT	Sternum only	IIB	NS	high dose CT followed by Auto-SCT	Not available
12	Priola et al., [3]	2006	20	M	primary	eosinophilic granuloma, IHC revealed HL	Y	-	Sternum, left supraclavicular LN	NA	NS	6XABVD followed by RT	Alive at 32 months
13	Daizyreena et al., [13]	2006	18	M	primary	HL	Y	-	Sternum and supraclavicular LN			chemotherapy	Alive (on treatment)
14	Langley et al., [14]	2008	7	M	primary	TB	Y	ATT	Sternum (3 cm), L1 Vertebra, left sacroiliac joint, right acetabulum	IV	NA	chemotherapy (UKCCSG guidelines)	Alive
15	Biswas et al., [5]	2008	21	M	primary	TB	Y	6 months ATT	Sternum (10x8 cm), left cervical LN, liver, spleen, abdominal LN	IVB	NS	6XABVD followed by RT	Progressive disease managed by 3xICE regimen Alive at 3 months
16	Oshikawa et al., [15]	2009	28	M	primary	HL	y	-	Sternum, right ilium, rib, left scapula	IV	MC	6XABVD followed by RT to the ilium	Alive
17	Goyal et al., [16]	2015	25	F	primary	LCH	Y	RT with Vinblastine	Sternum (5x5 cm) with axillary, supraclavicular, pre-vascular, anterior diaphragmatic LN and splenic involvement	IIIBS	NS	initially received RT with vinblastine for LCH, later received 8x ABCD for stage IIIBS HL	Alive at 1.5 years
18	Singh et al., [17]	2015	30	F	primary	TB	Y	5 months ATT	Sternum, cervical LN, pleural effusion, HSM, ascites, pre and para-aortic LN	NA	MC	1XABVD	Died after 1 cycle of chemotherapy

[Table/Fig-5]: Table showing clinical details of all the cases of sternal Hodgkin's lymphoma reported in the English literature from 1966-2015.

*M-male, F-female, HL-Hodgkin's lymphoma, TB-tuberculosis, LCH-Langerhan cell histiocytosis, Y=yes, NS-Nodular sclerosis, MC-Mixed cellularity, RT-radiotherapy, LN-lymph node, NA-not available, ATT-anti-tubercular therapy, COPP- Cyclophosphamide/ vincristine/ procarbazine/ prednisolone, ABVD- adriamycin/bleomycin/vinblastine/dacarbazine, PS-performance status, ICE- Ifosphamide/carboplatin/etoposide, CT-chemotherapy, SCT-stem cell transplantation.

at initial presentation as well as at relapse. Disease recurred in our case probably because she didn't receive RT after chemotherapy during initial treatment. Since late relapse remains chemosensitive to the initial therapy, combined chemo-radiotherapy brought complete remission in the patient.

CONCLUSION

Present case along with literature review highlights the fact that Hodgkin's lymphoma should be kept in the differential diagnosis of a sternal mass and a high index of suspicion must be maintained

in such cases due to approximately a 40% chance of misdiagnosis on histopathological examination. Use of immunohistochemistry as a tool for definitive diagnosis is strengthened here. Combined chemo-radiotherapy for treatment of 'isolated sternal HL' is strongly advocated.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Feb 20, 2016**

Date of Peer Review: **Apr 06, 2016**

Date of Acceptance: **Apr 18, 2016**

Date of Publishing: **Jun 01, 2016**