ALK POSITIVE PRIMARY EXTRANODAL ANAPLASTIC LARGE CELL LYMPHOMA MASQUERADING AS A SOFT TISSUE SARCOMA: A CASE REPORT

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Abstract:
Anaplastic Large Cell Lymphoma (ALCL) is a rare type of T-cell null cell Non Hodgkin Lymphoma. It is seen predominantly in children and young adults. Some of these tumors express an enzyme called Anaplastic Lymphoma Kinase (ALK) produced by the alk gene, an oncogene. The disease can present purely nodally or with extranodal involvement. Extranodal involvement can mimic a soft tissue sarcoma. Purely extranodal presentation is very rare and most of these are ALK-ve ALCL than ALKpositive ALCL. We present a case of a primary extranodal ALK positive Anaplastic Large Cell Lymphoma that presented clinically as a soft tissue sarcoma in a 56-year-old female.

Keyword: Anaplastic Large Cell Lymphoma, ALK positive, extranodal, sarcoma

INTRODUCTION:
Anaplastic large cell lymphoma (ALCL) is a rare disease comprising less than 5% of all cases of Non Hodgkin lymphoma. The definition of Anaplastic Large Cell Lymphoma (ALCL) has evolved since its original description in 1985 by Stein et al. as a lymphoma characterized by large anaplastic lymphoid cells with uniform, strong expression of CD30 and a tendency to grow cohesively and invade lymph node sinuses. Subsequent immunophenotypic and genetic studies resulted in restriction of the diagnosis to cases of T-cell or null cell lineage, and recognition that primary cutaneous and systemic types were clinically and immunophenotypically distinctive. The current World Health Organization (WHO) classification of hematopoietic and lymphoid neoplasms published in 2008, distinguishes systemic ALCL from primary cutaneous ALCL.

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ALCL is categorized into 2 entities based on the expression of anaplastic lymphoma kinase 1 (ALK-1), a tyrosine kinase receptor, into ALK positive ALCL and ALK negative ALCL. ALK positive cases have a male preponderance and occur most commonly in children and young adults, whereas ALK-ve ALCL arise most commonly in the 5th and 6th decades. Extranodal presentation is uncommon. They are more commonly ALK+ve than ALK-ve. While ALK+ve ALCL has a predilection for sites such as skin, soft tissue, bone, lung and liver, ALK-ve ALCL predilection for the skin, liver, lung, GI tract and breast. Purely extranodal ALCL is rare and may mimic a sarcoma, clinically. We present one such purely extranodal ALCL that was ALK+ve and mimicked a sarcoma clinically.

CASE REPORT:
A 56-year-old female presented to the surgery out-patient clinic with complaints of a growth in the right inguinal region of 15 days duration, which was associated with pain and fever since a week. Her past medical history was unremarkable. Local examination revealed a fungating mass of about 15 X 8 X 4 cm size on the medial side of right thigh, in the subcutaneous plane. There was local redness, tenderness and induration with palpable inguinal nodes. MRI revealed a soft tissue tumor in the anteromedial aspect of right thigh and right inguinal lymphadenopathy with no obvious infiltration into the surrounding muscles. There was no lymphadenopathy at any other site, either clinically or radiologically. Hence a diagnosis of a soft tissue sarcoma was made by the consultant surgeon. An initial ulcer edge biopsy showed features suggestive of reactive hyperplasia with fibroblastic granulation tissue. The patient was then posted for wide excision and per-operatively, the mass was found adherent to the Sartorius muscle with multiple enlarged inguinal nodes. The mass was excised along with overlying skin and subcutaneous tissue and sent for histopathological examination. On gross examination, the specimen was a skin covered soft tissue mass, measuring 20 x 15.5 x 8 cm. The skin showed a nodule with ulceration measuring 8 x 7 x 4.3 cm. There was adequate skin clearance around the nodule. The posterior surface showed adipose tissue, skeletal muscle and whitish firm areas. Cut surface showed a poorly circumscribed yellow white tumour of size 10.5 x 9 x 7 cm with areas of hemorrhage and necrosis. The tumour was located 3mm from the deepest dissection margin. 13 lymph nodes were also identified whose size ranged from 0.5cm to 1.3cm in greatest diameter. They were not fleshy and did not show areas of necrosis. Microscopy showed skin with an underlying expansive neoplasm in the subcutaneous tissue, which was poorly circumscribed. The skin showed surface ulceration, irregular acanthosis and patchy mononuclear cell infiltration. The neoplasm was composed of poorly cohesive cells which showed alveolar pattern of arrangement, in some areas. The cells were dyscohesive and pleomorphic. Some of the cells appeared plasmacytoid. The nuclei displayed anisokaryosis, irregular indentations of nuclear membrane, coarsely clumped chromatin and single nucleolus (Fig 1, H&E). Tumour giant cells (uni, bi and multinucleate) and numerous mitotic figures (16-20/HPF in the most cellular areas) were noted. The tumour was found infiltrating the dermis and ulcerating the epidermis. Infiltration of subcutaneous adipose tissue and skeletal muscle bundles was seen. Areas of necrosis with secondary microcalcifications were also seen. The posterior and lateral resected margins were free of tumour.
Lipoblasts and rhabdomyoblasts were not seen. There were 13 lymph nodes which showed nonspecific reactive hyperplasia. A provisional diagnosis of Non-Hodgkin lymphoma - high grade, was made prior to immunohistochemical studies. Immunohistochemical marker studies showed that the tumor cells were positive for Leukocyte Common Antigen (Fig 2) and CD30 (Fig 3). Immunohistochemical study for ALK (anaplastic lymphoma kinase 1) performed subsequently, was also found to positively expressed (Fig 4). The tumor cells were negative for CD3, Desmin, Cytokeratin and CD99. All the lymph nodes studied showed features of chronic non-specific hyperplasia. CD30 was run on all of them to identify if ALCL cells were present. However it was negative on all the 13 lymph nodes.

Fig 1: H&E stained section showing large, pleomorphic tumor cells with occasional 'Hallmark" cells (arrow)

Fig 2: Tumor cells are positive for LCA IHC marker

Fig 4: Tumor cells showing diffuse and strong positivity for IHC marker, ALK.
DISCUSSION

Anaplastic large cell lymphoma (ALCL) was originally designated as Ki-1 Lymphoma in 1985 by Stein et al, based on the uniform positivity to Ki-1 antibody. Subsequently understanding of ALCL evolved and was recognized to be a T-cell/ null-cell lineage, with expression of CD 30. Discovery of t(2;5) that expresses the ALK (anaplastic lymphoma kinase 1 ) protein constituted a distinctive group designated as ALK+ve ALCL or ‘ALKoma’. In 2001, the World Health Organization (WHO) stated that the diagnosis of ALCL included two subsets which either express or don't express the ALK protein. According to WHO 2008 edition of hematopoietic and lymphoid tumors, ALCL represents approximately 3% of adult and 10-30% of childhood Non Hodgkin Lymphomas, and in Asia the overall incidence and frequency are much lower. The pathogenesis of ALK+ve ALCL is due to a molecular abnormality involving ALK, located at chromosome 2p23 that leads to over expression of ALK. Nine different abnormalities have been reported till date, and of these, t (2;5) (p23; q35) is the most common. The cells of ALCL have a broad morphological spectrum. However “Hallmark cells” are characteristic in most cases and types of Anaplastic Large cell Lymphoma. These cells are large with eccentrically placed embryo-like or reniform nuclei, with a distinct eosinophilic Golgi zone adjacent to the nucleus. Smaller cells with similar morphology can also be seen. Occasionally, nuclear inclusion-like bodies may be seen, which are not true inclusions, but invaginations of the nuclear membrane. Such cells have been referred to as “Doughnut cells”. The nuclear chromatin is usually finely clumped or dispersed with multiple small basophilic nucleoli.

Several variants have been recognized, but they have not been shown to have any prognostic significance. These include the Classical (70-80%) variant, Monomorphic variant, Lymphohistiocytic variant, Small cell variant, Mixed cell variant, Hypocellular variant, Giant cell variant and the Sarcomatoid variant. The classical variant shows neoplastic cells cohesively forming clusters and sheets. The cells may be highly pleomorphic having horse-shoe shaped nuclei with a paranuclear hof and prominent nucleoli. The mitotic rate is high and atypical mitotic figures are common.

Immunohistochemically both the ALK positive and ALK negative ALCL are characterized by positivity for CD30 which is expressed as intense membranous and paranuclear dot pattern staining (golgi region), imparting a target-like appearance. Most cases of ALK+ve ALCL express T-cell or T-cell associated antigens such as CD2, CD4, CD7, CD43 and CD45 RO. Null-cell type of ALK+ve ALCL lack expression of any of these T-cell or T-cell associated antigens. ALK+ve ALCL also show frequent expression of EMA. In a review of 87 cases of ALK+ve ALCL, Keery J Savage et al observed that the median age at diagnosis was 34 years with a slight male preponderance. 54% were purely nodal while in the remainder there was extranodal involvement as well. Common extranodal sites of involvement are bone, bone marrow, subcutaneous tissue, spleen etc. In another large study by Eric Jacobsen, he observed that there was a marked male predominance of ALK+ve ALCL with male-female ratio of 6.5:1.
There are many case reports of primary cutaneous ALCL (now known as Primary Cutaneous CD 30 positive T cell lymphoproliferative neoplasms) which involve the skin, dermis and extend into the subcutaneous tissue. There are sporadic case reports of primary extranodal ALCL which mimicked a sarcoma. These cases were ALK –ve usually. For instance primary ALCL of breast was reported by Emilio M Pereira et al\(^6\), while Komal Galani et al described a primary ALCL of the rectum\(^7\).

The presenting feature of the index case is noteworthy for an ALK+ve ALCL to have presented as a primary extranodal lesion. In summary, we describe a rare primary extranodal ALCL that was ALK+ve and not having spread to the 13 regional lymph nodes studied. The correct diagnosis was facilitated by a vigilant morphological observation of the neoplastic cells and by appropriate immunophenotypic analysis. This patient was treated at the oncology clinic of the hospital, but died within 3 months of diagnosis. This indicates that such lesions are much more fatal than the descriptions in literature.


6 Emilio M. Pereira, Sueli A. Maeda and Jorge s. Reis -Filho. Sarcomatoid Variant of Anaplastic Large Cell Lymphoma Mimicking a Primary Breast Cancer. Arch Pathol Lab med – vol 126, 6, June 2002.