

Hodgkin's Disease in Children-A Clinical Case

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Abstract: Many head and neck disease processes manifest themselves as neck masses- congenital, inflammatory, and neoplastic diseases. Lymphoma is the primary malignant neoplasm of lymphoid tissue. Hodgkin's disease has been considered a rare disease in the pediatric age group but the possibility of it should not be excluded. Failure of regression of a cervical lymphadenopathy after 4–6 weeks might be an indication for a diagnostic biopsy. If there is any suspicion of malignancy or in cases of persistent lymphadenopathy an excisional biopsy with microscopic examination of the lymph node should be performed. In this paper we report a case of Hodgkin's lymphoma of the head and neck region in childhood in which the generally accepted algorithm of diagnosis and behavior regarding a non-specific lymphadenopathy was neglected. The biopsy and the diagnosis were delayed and the possibility of neoplastic disease was underestimated. We present also a review of the related literature.

Keywords: cervical lymphadenopathy, Hodgkin lymphoma, children

1. Aim

We present a case of Hodgkin's disease in childhood with the purpose to show the possibility of development of neoplastic disease even in this early age and to highlight the need for formal management guidelines for cervical lymphadenopathy so that the diagnosis is not delayed.

2. Introduction

Many head and neck disease processes manifest themselves as neck masses-congenital, inflammatory, and neoplastic diseases.[12] In the children group there is a higher incidence of congenital abnormalities and infectious diseases and relative rarity of malignancies. [13,17] The prevalence of malignant lymphadenopathy increases with age and is higher in patients with known malignancy. The most common causes of malignant cervicofacial lymphadenopathy are lymphoma and metastatic squamous cell carcinoma. [16]

Patients with cervicofacial lymphadenopathy are referred to a variety of specialists, including maxillo-facial surgeons; ENT and general surgeons; hematologists; oncologists; and pediatricians. [16] These conditions are treated by surgical excision except for some inflammatory masses, and often, those too may be excised for diagnostic reasons. If the etiology of the mass stays difficult to find and if the history, physical examination, and routine diagnostic tests do not lead to a final diagnosis, any unknown neck mass, particularly a unilateral, asymptomatic mass corresponding to the location of known lymph node groups, must be considered a neoplastic lesion until proved differently. [12] Failure of regression of a cervical lymphadenopathy after 4–6 weeks and after a trial of antibiotic therapy might be an indication for a diagnostic biopsy. [10,19] Quick and early diagnosis is essential. [16]

3. Case Report

We present a clinical case of a 16-years old female that presented with a palpable mass in the left cervical area. (Fig.1)



Figure 1: Left cervical lymphadenopathy

The reported lymphadenopathy persisted more than 6 months. At the manifestation of the lymphadenopathy, the child was consulted with oral and maxillofacial surgeon who recommended surgical exploration of the pathologically enlarged lymph node for diagnostic purpose. Multiple consultations with hematologists were completed; all of the hematologic tests had normal values and did not correspond with hemolymphoid pathology. The disease had progressive evolution. There was an increase of the number and enlargement of the lymph nodes leading to formation of packets. Since she showed no evidence of resolution, she was referred again in the OMFS Department for surgical exploration of the neck masses. The generally accepted algorithm of diagnosis and behavior regarding a non-specified lymphadenopathy was neglected and the biopsy and the diagnosis were delayed. The possibility of neoplastic disease was underestimated. All hematologic tests were within normal limits. The MRI of the head, thorax, abdomen and pelvis showed conglomerates of lymph nodes of 3 submandibular and at least 4 deep and 2 superficial lymph nodes in the left. (Fig.2)



Figure 2: Left cervical lymph nodes after extirpation

All the masses had a uniform signal intensity and showed expansive (not infiltrative) growth pattern. The masses showed moderate compression on the adjacent structures. All other cervical lymph node and all other lymph collectors in the studied area showed no pathological enlargement. No alteration in the medulla of all bones in the studied area were detected. A chest X-rays was performed, and showed no abnormalities- no hilar lymph node enlargement was seen. The histology of the explored cervical lymph nodes showed classic Hodgkin's lymphoma, mixed cellularity type with an initial transition to nodular sclerosis type. The child is referred to PET/CT scan for staging and subsequent treatment.

4. Discussion

Cervical lymphadenopathy is a frequent problem in children because of the relative increase in lymphoid tissue.[10,17] The condition most commonly represents a transient response to a benign local or generalized infection, but occasionally it might announce the presence of a more serious illness.[10] The main causes of lymphadenopathy in the pediatric group are: bacterial, viral, protozoal and fungal infections, malignancies including Hodgkin's lymphoma, leukaemia, metastases. Enlarged lymph nodes may also follow systemic lupus erythematosus, juvenile rheumatoid arthritis, histiocytosis, Kawasaki disease, collagen vascular disease, sarcoidosis, and may appear post vaccination or after some drugs intake (e.g. phenytoin).[13,17] Management algorithms in case of generalized lymphadenopathy have been created, but there are not still official guidelines for persistent cervical lymphadenopathy in children.[13,17] Treatment of cervical lymphadenopathy depends on the underlying cause. Most cases of lymphadenopathy are self-limited and does not require any treatment other than observation. The treatment of acute bacterial cervical lymphadenitis without a known primary infectious source must offer appropriate coverage for both *S. aureus* and group A β -hemolytic streptococci. When the

primary source of infection is identified, the therapy have to be conducted empirically against the microorganism most frequently associated with that source, until waiting for the results of the culture and sensitivity tests to be ready.[10] Lack of regression of the unexplained lymphadenopathy after 4–6 weeks and after a trial of antibiotic therapy or if there is any doubt of malignancy, is a clear mark for a diagnostic biopsy.[3, 13,19] In order to provide adequate tissue for examination, an incisional or excisional biopsy is preferred, but a core-needle biopsy can be considered when excisional biopsy is not possible.[3,19]

Lymphoma is the primary malignant neoplasm of lymphoid tissue, and is considered as the third most common cancer in children worldwide.[1] Lymphomas mostly involve lymph nodes, spleen and other non-haemopoietic tissues.[5] The two categories of lymphomas, non-Hodgkin's lymphoma (NHL) and Hodgkin's disease (HD) have different clinical manifestations, microscopic morphology, treatment, and prognosis.[1] HLs predominantly involve the lymph nodes and only around 5% appear in extranodal sites, in contrast to 30% of NHL cases presenting in extranodal sites. [20]

The first report on Hodgkin's disease in children was presented by Thomas Hodgkin in 1832. In 1902, Dorothy Reed described another 4 cases. Since then, a lot of studies have dealt with the histology, incidence, epidemiology, and prognosis of HD in childhood.[15]

Hodgkin's disease has been considered a rare disease in the pediatric age group.[2] It is extremely rare in the very young. Its occurrence increases progressively with age all over the pediatric group and into young adulthood. [21]

In childhood HD exhibits certain features that differ significantly from the disease when seen in the adults. [21]

Many previously held international studies have shown male prevalence. In the study of Al-Samawi et al. 72.3% of the affected were male, and the male to female ratio was 2.6:1, which appears similar to the previous findings reported in the literature in all ages of HD. [1] The male predominance in childhood Hodgkin's disease only starts to diminish from age 12 upward, demonstrating possibly a transition into the pattern of the disease in young adults. The noticeable sex difference has never been explained. [21] The predominantly male population involved by Hodgkin's disease in the first decade of life tends to support a possible hormonal effect of unknown nature on host susceptibility to the disease. Some additional studies supporting this theory should be undertaken. [18]

Two international symposia have been conducted to create guidelines for the study and care of patients with Hodgkin's disease. The Rye Conference in 1965 focused attention on the role of histopathologic classification in prognosis and put the basis for the classification of staging in relation to the extent of the disease; the Ann Arbor Conference (1971) stressed newer techniques of assessing the extent of disease. [2,14]

Staging defines disease location and extent, suggests prognostic information, allows comparisons among studies,

and provides a baseline against which response or disease progression can be compared. Initial staging criteria were designed mostly for Hodgkin lymphoma (HL) and were displaced by the Ann Arbor classification, which subdivided HL patients into 4 stages and the subclassification A and B based on the absence or presence of fevers to greater than 101°F (38.3°C) during the previous month, unexplained weight loss more than 10% of body mass over 6 months, and night sweats during the previous month. Ann Arbor classification has been the most widely used classification since its introduction. [3,6,11] The stages of the disease in children are the same as in adults. [9]

The four-stage system in localized and generalized Hodgkin's disease is as follows:

Stage I:The disease is limited to one lymph node-bearing region or one extranodal site, exclusive of liver, bone marrow, or diffuse involvement of extranodal sites.

Stage II:The disease is limited to one side of the diaphragm, i.e., to lymph node-bearing regions, including associated involvement of one extranodal site, or including direct invasion of adjacent structures related to the principal lesion.

Stage III:The disease involves lymph node-bearing regions on both sides of the diaphragm with or without, associated involvement of one extranodal site, or direct invasion of adjacent structures.

Stage IV:The disease has generalized beyond Stage III to diffusely involve extranodal sites.[6]

PET-CT scanning is particularly important because it enhances the precision of staging compared with CT scans for nodal and extranodal sites. [3]

The prime cellular trait in the making of a histopathologic diagnosis is often the presence or absence of Reed-Sternberg cells. [19] The Reed-Sternberg cell is a lymphoid cell, in most cases a B cell, and it is clonal. Hodgkin's disease is thus a true lymphoma.[7]

On the basis of a combination of immunophenotype and morphologic features, the Revised European-American classification system recognizes two main types of HL: classical types (nodular sclerosis, mixed cellularity, lymphocyte-rich classical HL, and lymphocyte depletion) and nodular lymphocyte-predominant type. These two types probably are distinct biologic entities. [4,7,14]

There are differences in the frequency of histologic types seen in Hodgkin's disease in the pediatric age group as compared to the adults. [21] Strum and Rappaport highlighted the high incidence of the nodular sclerosis and lymphocyte predominance types in childhood: these features constituted more than 90% of all cases.[15] The majority of cases, regardless of classification, were characterized by a noticeable predominance of mature lymphocytes and an insufficiency of Reed-Sternberg cells. These findings suggest that a particular host response characterizes the disease in the young. [18] In the study of Poppema and al.

62% of the cases were found to be of these prognostically favorable subtypes- nodular sclerosis and lymphocyte predominance types. This is comparable to the results of Butler, who reported a proportion of about 50%. [15] 40% of the children studied by Young et al had nodular sclerosing Hodgkin's disease, a frequency similar to that in adults. [21] In the study of Jenkin et al, the overall percentage distribution was nodular sclerosis-57%; mixed cellularity- 28%; lymphocytic predominance-14%; and unclassified-1%. Lymphocytic depletion was not seen.[8] The histologic patterns of Hodgkin's disease in children also seem to vary from country to country. For example, in contrast to Europe, there is the experience in Africa and South America, where several investigators have noted a predominance of lymphocyte-depleted patterns, as well as an overall increased frequency of the disease in children. [21] Progression usually occurs toward a histologically more malignant form of HD, while the reverse is rarely possible. [1]

Even histologically, some difficulties in diagnostic HL may arise. For example, a cat-scratch disease or toxoplasmosis can induce changes in the reticulum cells that are similar to those of Hodgkin's disease or patients treated with hydantoin for epilepsy may show a reticular hyperplasia. [19]

The treatment schemes in the management of this disease vary widely.[9] The treatment of HD in children is the same as in adults: (1) Radiotherapy for local lesions in stage I and II, generally along with "prophylactic" irradiation of adjacent areas; (2) Chemotherapy with one or several drugs for generalized or diffuse disease, followed if needed by local irradiation. [19] X-ray therapy in tumoricidal dosage still seems to be the best treatment for HD. This treatment is most successful with patients in stages I or II. [19]

Hodgkin's disease is in all probability unifocal in origin and treatable when limited to one lymph node area. [9] With these cases, very long survival or even complete cure may be looked for. This fact draws attention to the importance of establishing the diagnosis as early as possible. Prognosis is poor for patients in stages III and IV. The combination of chemotherapy with X-ray therapy gives some hope of improvement but its aggressive use may cause some serious complications to the growing child. [14,19] The closure of skeletal growth centers and permanent neurologic deficit are the two of the most important associated complications. [14] The findings of the study of Norris et al. suggest that the histopathologic type and clinical stage do have an effect on the prognosis. Children with less extensive disease (Stage I or IIA) or more favorable histopathologic type (lymphocyte predominance) have a better chance of long-term survival. The children with more advanced disease and less favorable histopathologic type require more intensive therapy, even at the risk of complications arising from therapy. [14] The relapse of the Hodgkin's disease, in the long run, is a bad prognostic factor.[8]

5. Conclusion

Cervical lymphadenopathy is a common and usually benign finding but one must never forget the possibility of

development of neoplastic disease such as Hodgkin's disease despite its relative rarity. Clinical history, physical findings, and laboratory and radiologic investigations may give important data for establishing a proper diagnosis. Some cases require excisional biopsy for the definite diagnosis. Today the advances in treatment techniques for Hodgkin's disease have enhanced the survival rate for these patients. The treatment is compatible with the extent of the disease. Hodgkin's disease is probably unifocal in origin and treatable when located in one lymph node area, in which cases very long survival or even complete cure may be expected. This fact stresses on the importance of establishing the diagnosis as early as possible.

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