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Hodgkin's Disease and its Oral Manifestations

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Abstract: The Hodgkin's disease, also known as Hodgkin's lymphoma, is a cancer of the lymphatic system. Its origin, pathogenesis and characteristics cell constitution are clear as also the diagnostic algorithm and the therapeutic manage. The aim of this research is to describe the oral manifestations of the disease: Complications of the treatment or lesions associated to other diseases as disckeratosis congenital or the follicular lymphoid hyperplasia of oral cavity. These associations have been studied even if their pathogenetic mechanisms are unclear. It's also important, in dentistry, the confirmed association with the Sjogren syndrome and the primary manifestation of the Hodgkin's lymphoma in the parotid gland, which is possible and reported in literature but rare and actually object of research.

Key words: Hodgkin's disease, hodgkin's lymphoma, Reed's Sternberg cells, disckeratosis congenital, follicular lymphoid hyperplasia, Sjogren syndrome, paraneoplastic lesions

INTRODUCTION

Hodgkin's disease, also known as Hodgkin's lymphoma, is a cancer of the lymphatic system. Its origin, pathogenesis and characteristics cell constitution are clear as the diagnostic algorithm and the therapeutic manage. The oral manifestations are, generally, object of research (Herrin, 1999). Xerostomia, radiation-induced caries, osteoradionecrosis and reduced immune response to microorganisms for example to the infection by candida can be included among the complications. It's also important, in dentistry, the confirmed association with the Sjogren syndrome and the primary manifestation of the Hodgkin's lymphoma in the parotid gland considerated possible and reported in literature, but rare still and actually object of research.

The Hodgkin Lymphoma (HL) is, by definition, a disseminated or located malignant proliferation of tumoral cells primarily derived from the lymphoreticular system, involving the lymphonodal fabric and the bone marrow. Unlike other lymphoma, whose incidence increases with age, Hodgkin's lymphoma has a bimodal incidence curve. It occurs most frequently in two separate age group, the first being young adulthood (age 15-35) and the second being in those over 60 years old. Overall, it is more common in men, except for the nodular sclerosis variant, which is more common in women. The annual incidence of Hodgkin's lymphoma is about 1/25,000 people, and the disease accounts for slightly less than 1% of all cancers worldwide. The origin of the neoplastic cells Reed's Sternberg (R-S), characteristic cells of this lymphoma, are extremely controversial, especially because these cells don't express the classical markers of the lymphocytes. However, the studies have underlined that these cells are interested in the rearrangements of the genes of the immunoglobulins with somatic ipermutations, establishing that the cell of origin is a cell B of a germinal centre or post germinal. In rare cases (1-2%) they derive instead from T cells transformed. An important sign is the frequent presence of the episomes of the Epstein Barr Virus (EBV) in the cells RS. It seems that in some cases the infection from EBV can save cells destined to the apoptotic process setting them in a proper stadium to acquire other mutations still ignored that collaborate to the malignant transformation (Murray, 2003). From the pathogenetic point of view, it is recorded a characteristic accumulation of reactive cells introduces them in answer to cytokine secreted by the cells R-S. Once attracted, the reactive infiltrator supports the growth and the tumoral cells surviving. From the view anatomic-pathological point of the lymphoma of Hodgkin is a neoplasia with the peculiar characteristics as the tumoral cells notes as cells of Reed-Sternberg, they are rare and absorbed in a predominant reactive cellular infiltrator constituted by granulocytes, plasma cells, lymphocytes T, histiocytes, eosinophils. During the years the origin of the neoplastic cells of the HL has remained wound by a halo of mystery; they has been considered by time as originated from the macrophages, from the histiocytes, from the dendritic follicular cells, the interdigitated reticular cells, the

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granulocytes, the lymphocytes B or the lymphocytes T. Today, it's definitely accepted their origin from the peripheral lymphocytes B even if, rarely originated from lymphocytes T. The classical cells of R-S are also defined diagnostic of the LH, but not pathognomonic because it can also be observed in reactive processes as viral diseases, or other primitive and secondary neoplastic lesions of the lymph nodes; they are introduced as great cells in possession of a bilobed nucleus with a eosinophils nucleolus well evident and thickened nucleate membrane (Vadmal *et al*., 2000). The uncertain origin of the neoplastic cells and their rarity have baited an intense debate on the neoplastic or infective nature of the HL, today the debate can be consider concluded after the definitive recognition of the malignant tumoral nature of the HL and its origin from the peripheral lymphocytes B. A curious aspect of this conclusion is that there is now accord, nearly unanimous, which consider the HL as an neoplastic disease of possible infective origin, at least in a certain part of the cases (Bosq *et al*., 2002; Cavalieri *et al*., 2002).

CLASSIFICATION

The classification WHO recognizes five subtypes of LH:

- Nodular sclerosis;
- Mixed cellularity;
- Lymphocyte rich;
- Lymphocyte depletion;
- Nodular lymphocyte-predominant.

In the first 4 subtypes the cells R-Ss have a similar immunophenotype gathering these forms in the so-called classical LH. The type nodular sclerosis is the most common form of LH, constituting the 65-70% of the cases. It is characterized by a variation of the cell RS, the lacunar cell, and from collagen bands which divide the lymph node in circumscribed nodules. The fibrosis can be scarce or abundant, and the neoplastic cells are observed in a polymorphous background of small lymphocytes T, eosinophils and plasma cells (Abbes *et al*., 2002; Atasoy *et al*., 2006). This form has a propensity to interest the low cervical lymph nodes, sovraclavear or mediastinal of teen-agers or young adults and rarely is in partnership only to EBV. The prognosis is excellent (Table 1).

The systemic symptoms are constituted by painless swelling of lymph nodes in neck, armpits and groin, persistence fatigue, inexplicable fever (superior to the 38°C), which can be remittent, continuous or cyclical with periods of fifteen alternate days to periods without fever in the night time, night sweats, unexplained weight loss, loss appetite and itching. To define with precision the diagnosis it's essential the laboratory tests of blood and urine, chest X-ray, CT scan of the chest, abdomen and pelvis (Brice *et al*., 2001). The diagnostic confirmation of the lymphoma of Hodgkin can definitely get though the biopsy, which puts in evidence the cells of Reed-Sternberg in a characteristic histological disposition and the relief of reactivity of monoclonal antibodies with the cells of Red-Stenberg (Leu-M1 [CD15] e CD30 [Ber-H2]) to differentiate such disease from the lymphoma no-Hodgkin. The classification of Ann Arbor is important for the prognosis. It essentially depends by the stadium of the disease, by the histological type, by the possible alterations of some examinations of laboratory (above all LDH, beta 2-microglobulina), by the age of the patients, the general condition general of the patient and by the possible presence of concomitant diseases (Moghe *et al*., 2003; Quinones *et al*., 2005; Stewart *et al*., 2001) (Fig. 1-3). The presence of specific parameters it establishes the stadium of the classification of the limphoma of Ann Arbor in analysis and what therapeutic protocol it's better to use (Table 2).

According to the actual therapeutic protocols, the stadium of the cancer more than the histological type is the most important variable from a prognostic point of view. The percentages of recovery of patients with diseases in the stadium I or IIA it's near to 90%. Even in the advanced stadiums (IVA and IVB) it's obtained a survival without disease In a 5 years-long period of 60-70%. The greater part of the patients are treated with the chemotherapy and with the radiotherapy and they get good results while the autologous transplantation can treat the 50% of the patients that are physiologically eligible for intensification of therapy and responsive to the chemotherapy of lifesaving induction. The allogeneic transplantation is not shown better and it is not recommended. The autologous transplantation is object of study in patient selected to high risk to the diagnosis. Unfortunately, the treatment for Hodgkin's results in

Table 1: Hodgkin's disease-classification

Type	Histologic features	Frequency	Prognosis
Nodular sclerosis	Bands of fibrosis,lacunar cells	Most frequent type, more common in women	Good, most are stage I or II
Mixed cellularity	Composed of manydifferent cells	Most frequent in older persons, second most frequent overall	Fair, most are stage III
Lymphocyte predominance	Mostly B-cells andfew Reed-Sternberg variant cells	Uncommon	Good, most are stage I or II
Lymphocyte depletion	Many Reed-Sternberg cells and variants	Uncommon	Poor, most are stage III or IV

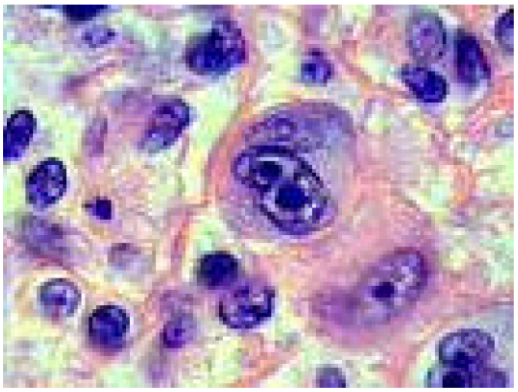


Fig.1: Clasic Reed Sternberg cells

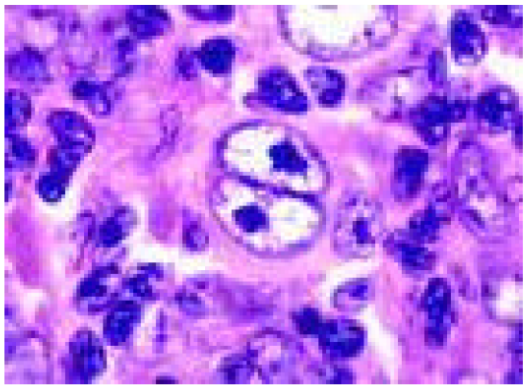
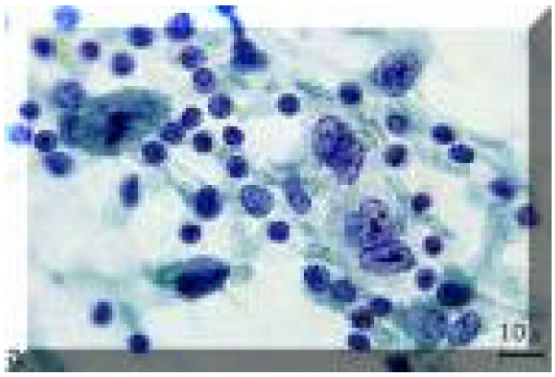
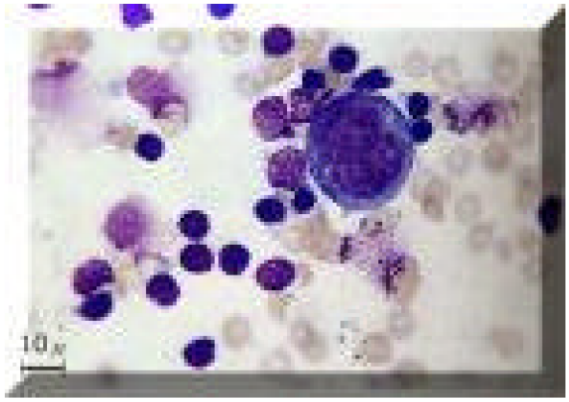


Fig. 2: Bilobed nucleus of Reed-Sternberg cell in Hodgkin disease



(a)



(b)

Fig. 3a, b: Reed-Sternberg cells in a hodgkin lymphoma

Table 2: Hodgkin's disease-staging

Stage	Characteristics
I	Only a single lymph node site or extranodal site is involved .
II	Two or more lymph node sites on one side of the diaphragm are involved, or limited contiguous extranodal site involvement.
III	Lymph node sites on both sides of the diaphragm are involved, with splenic or limited contiguous extradodal site involvement, or both.
IV	Extensive involvement of extranodal sites, with or without lymph node involvement.

significant, permanent complications that persist for the duration of the patient's life.

ORAL COMPLICATIONS

The complications can include xerostomia, radiation-induced caries, the risk of osteoradionecrosis in irradiated bone, and systemic complications such as a reduced immune response to microorganisms for example the infection by candida.. These patients can undergo all types of dental treatment safely as long as the practitioner recognizes the risks involved and takes appropriate precautions. The inflammatory gingival overgrowth, premature root resorption of deciduous teeth and alveolar bone loss in conjunction with the regression of gingival overgrowth which followed the completion of chemotherapy, are strongly indicative of a paraneoplastic manifestation of HL in the child (Nicolatou *et al*., 2001). The gingival inflammatory reaction was probably further aggravated by the bacterial-stimulated cytokine secretion released by monocytes. From a lot of time it is object of study the association between Hodgkin's disease and diskeratosis congenita. For definition, disckeratosis congenita is a rare, hereditary, multisystem disorder characterized by abnormalities of the skin, nails and oral mucosa, pancytopenia and increased incidence of different type of neoplasias one which is the Hodgkin's disease (Baykal *et al*., 1998, 2003). Besides, it's reported in literature an unusual case of mixed cellularity classical Hodgkin's lymphoma with prominent involvement of the base of the tongue and also this lesions is object of study to find a possible association with a prognostic value (Treaba *et al*., 2006). Recently, it is reported in

literature a case of Follicular Lymphoid Hyperplasia (FLH) of the oral cavity presenting a Progressive Yransformation of Germinal Center (PTGC) (Kojima *et al*., 2005). The PTGCs contained a few large lymphoid cells resembling lymphocytic and histiocytic Reed-Sternberg cells of nodular lymphocyte-predominant Hodgkin lymphoma and demonstrated strong expression of Epstein-Barr Virus (EBV)-encoded small RNA in scattered large lymphoid cells in the PTGC. This study confirm that the FLH of the oral cavity appears to be an EBV-associated lymphoproliferative disorder but the present of the RS cells peculiar of the HL is unclear. Finally, in the description of the oral lesions or diseases associated with HL is important remember the association between Sjogren Syndrome (SS) and Hodgkin's lymphoma. Patients with Sjogren syndrome are at increased risk of lymphoma development (Navarro *et al*., 2001; Tonami *et al* ., 2003). Because most lymphomas initially involve the neck organs, including the lymph nodes, meticulous imaging studies mainly focused on the cervical regions are recommended in the follow-up of patients with Sjogren syndrome. Finally, the primary manifestation of the Hodgkin's lymphoma in the parotid gland, which is possible and reported in literature but rare and actually object of research (Yancha, 2002).

CONCLUSION

The Hodgkin's disease is an important neoplasia of the lymphonodal system and its oral manifestation can be complication of the treatment or associated lesions.These complications can include xerostomia, radiation-induced caries, osteoradionecrosis and reduced immune response to microorganisms for example the infection by candida. The inflammatory gingival overgrowth, premature root resorption of deciduous teeth and alveolar bone loss in conjunction with the regression of gingival overgrowth are characteristics paraneoplastic manifestation of HL in the children. A possible associations between diskeratosis congenital and HL is reported in literature but not confirmed as, also, the possible association with the follicular lymphoid hyperplasia of oral cavity and the Sjogren syndrome.

REFERENCES

Abbes, I., K. Mrad and S. Sassi, 2002. Primary Hodgkin' s disease of the nasopharynx: A rare but bona fide disease; Pathologica, 94: 314-316.

Atasoy, BM., U. Abacioglu, O. Ozturk, R. Ozdemir and T. Tecimer, 2006. Hodgkin's disease in the nasopharynx. J. BUON., 11: 529-531.

Baykal, C., N. Buyukbabani and A. Kavak, 1998. Dyskeratosis congenita associated with Hodgkin's disease. Eur. J. Dermatol., 8: 385-387.

Baykal, C., A. Kavak, P. Gulcan and N. Buyukbaban, 2003. Dyskeratosis congenita associated with three malignancies. J. Eur. Acad. Dermatol. Venereol., 17: 216-218.

Brice, P., A. Guermazi and E.E. de Kerviler, 2001. Extranodal Hodgkin disease: Spectrum of disease; Radiographics, 21: 161-179.

Bosq, J., S. Aloulou and H. Farhat, 2002. Hodgkin' s disease primarily involving the oropharynx: Case report and review of the literature. Hematol. J., 3: 164-167.

Cavalieri, E., A.P. Anselmo and L. Cardarell, 2002. Hodgkin' s disease of the nasopharynx: Diagnostic and therapeutic approach with a review of the literature Ann. Hematol., 81: 514-516.

Herrin, H.K., 1999. The oral implications of Hodgkin's disease. Gen. Dent., 47: 572-575.

Kojima, M., S. Nakamura, M. Iijima, T. Yoshizumi, N. Sakata and N. Masawa, 2005. Follicular lymphoid hyperplasia of the oral cavity representing progressive transformation of germinal center, APMIS., 113: 221-224.

Murray, P.G. and L.S, J.S. Young, 2003. Epstein-Barr virus and oncogenesis: From latent genes to tumors; Oncogene.

Moghe, G., A. Borges and C. Soman, 2001. Hodgkin' s disease involving Waldeyer' s ring: A study of four cases; Leuk Lymphoma, 41: 151-156.

Navarro, B., M. Yebra, J. Romero and D. Suarez-Massa, Med. Clin. (Barc), 2001. Hodgkin lymphoma associated with primary Sjogren's syndrome Med. Clin. (Barc) 5, 116: 636.

Nicolatou-Galitis, O., T. Papadaki, M. Moshovi, J.J. Kamma, C. van Vliet-Constantinidou, C. Tsoumakas, A. Kattamis and F. Tzortzatou-Stathopoulou, 2001. Gingival overgrowth as the initial paraneoplastic manifestation of Hodgkin's lymphoma in a child. A case report. J. Periodontol., 72: 107-12.

Quinones-Avila Mdel, P., A.A. Gonzalez-Longoria and J.H. Admirand, 2005. Hodgkin lymphoma involving Waldeyer ring: A clinicopathologic study of 22 cases, American Journal of Clinical Pathology.

Stewart, A., N. Molony and K. Ah-See, 2001. Hodgkin's and non-Hodgkin's lymphoma of the head and neck, Laryngoscope, 123: 651-656.

Treaba, D.O., J.W. Eklund, J. Wayne, B.P. Nelson and J.N. Winter, 2006. Classical Hodgkin's lymphoma presenting with tongue involvement: A case report and review of the literature. Clin. Lymphoma Myeloma, 6: 410-413.

Tonami, H., M. Matoba, Y. Kuginuki, H. Yokota, K. Higashi, I. Yamamoto and S. Sugai, 2003. Clinical and imaging findings of lymphoma in patients with Sjogren syndrome. J. Comput. Assist. Tomogr., 27: 517-24.

Vadmal, S., G. LaValle and B. DeYoung, 2000. Primary extranodal Hodgkin disease of the transverse colon. Arch. Pathol. Lab. Med., 124: 1824-1827.

Yencha, M.W., 2002. Primary parotid gland Hodgkin's lymphma. Ann. Otol. Rhinol. Laryngol., 111: 338-342.