Case report

Lymphomas of the head and neck in dermatological practice

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Abstract

The number of newly diagnosed cases of lymphomas of the head and neck region has been continually increasing over the recent years. The symptoms of these lymphomas are commonly similar to benign inflammatory diseases and thus frequently lead to clinical misdiagnoses. Many consultations, including dermatological one, and repeated tissue biopsies are often necessary because of the coexistence of necrosis and inflammation in the tumors. Biopsies should be deep enough – punch biopsies are not recommended. The classification of lymphomas has undergone dramatic changes with the increasing understanding and progress in immunohistochemistry and molecular biology. We describe five patients with lymphomas of oral and nasal cavities: 2 derived from B-cells, 2 from T-cells, and 1 from NK/T-cells. The initial presentation of these diseases often suggests an inflammatory process, such as an odontogenic inflammation, sinusitis or benign inflammatory process.

Key words: B-cell lymphoma, T-cell lymphoma, NK/T-cell lymphoma, oral cavity, nasal cavity.

Introduction

Neoplasms originating from lymphoid tissues comprise a diverse group of diseases, including Hodgkin's lymphoma, non-Hodgkin's lymphoma (NHL), multiple myeloma, and lymphocytic leukemia [1]. The exact etiology of lymphoid neoplasms remains unknown, although a variety of possible risk factors exists including severe immunosuppression caused by various medications as well as some infectious diseases [2-8]. Furthermore, environmental factors including industrialization, certain job specializations, smoking among other life style factors were also suspected to play a role in the pathogenesis of these lymphomas, although they are not fully confirmed [9-15].

Malignant lymphomas of the oral cavity are quite uncommon and account for 3.5% of all oral malignancies. The most common origin of these lesions is in the soft tissues, followed by the bones. Approximately 90%

of the malignant lymphomas are B-cell lymphomas, especially diffuse large B-cell lymphomas (DLBCL) [16]. Furthermore, other subtypes of lymphomas may be found in the head and neck area including other types of B-cell lymphomas, T-cell lymphomas [17-20] or NK/T-cell lymphomas (thought before to be the main type affecting the nasal cavity) [21].

The symptoms of lymphomas of the head and neck are commonly atypical and create various diagnostic difficulties. The aim of the study is to present problems encountered during the course of diagnosis of five patients with lymphomas of the head and neck who were consulted also by dermatologists.

Case reports

We present 5 cases of lymphomas of the head and neck with an emphasis on the diagnostic difficulties

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encountered during the treatment of these patients: 2 females (34- and 39-year-old) with a B-cell lymphoma, a 23-year-old male as well as a 16-year-old female with a T-cell lymphoma, and finally a 49-year-old female with an extranodal NK/T-cell lymphoma, nasal type. All patients were hospitalized at the Department of the Head and Neck Surgery of the Medical University of Gdansk. Hematoxylin-eosin (HE) staining of mucosa and immunohistochemistry of skin biopsy specimens with antibodies against CD2, CD3, CD4, CD5, CD8, CD19, CD20, CD45RO, and CD56 were performed. The patients' records were then analyzed for the course of the disorder and methods of the treatment.

Case 1

A 34-year-old white female presented with a 2-year history of lesions initially recognized as acute periostitis with unknown etiology. The patient had additionally complained of fever, lack of appetite, weight loss, and night sweats. Hyperthyroidism was ruled out as a differential diagnosis. A radiograph of the oral cavity revealed a reduced density of roots of teeth No. 22 and 23, nonetheless, a diagnosis of hypercementosis was given by the histopathologist. The tooth pulp appeared unaffected at that time, however, in approximately 5 months, necrosis of the pulp of tooth No. 23 as well as a lesion resembling a periosteal abscess was found. The following biopsy confirmed the presence of ostitis. The inflammatory infiltration of the mucosal surface of both maxillary sinus-

es was also observed in computed tomography (CT). The third histopathological biopsy performed after many consultations revealed a diffuse large B-cell lymphoma. A lymphadenopathy of submandibular lymph nodes was noted, while the chest and abdomen CT appeared unremarkable. The patient was treated with a standard protocol of chemotherapy (CHOP) and radiotherapy with good response. She was lost in follow up later.

Case 2

A 39-year-old white female presented with a 2-year history of edema of a cheek, with a formation of a small mass that was suspected to have benign inflammatory origin. The clinical picture suggested inflammation of the buccal lymph nodes or odontogenic inflammation. Due to the small size of the lesion, a total diagnostic excision was performed. The histopathological examination revealed a low-grade B-cell lymphoma. Six cycles of chemotherapy (CHOP) were introduced with a good therapeutic effect. The patient has been in remission since the completion of the treatment.

Case 3

A 23-year-old white male presented with a 3-month history of a painless deformation of the left maxilla (Figure 1). The patient denied any pain or tenderness of the lesion at the time of the initial office visit. A red-blue colored tumor began forming and enlarging progressively following removal of teeth No. 25 and 26, eventually extending from the suborbital to infranasal area. The oral mucosa was noted to be intact in the beginning (Figure 2). The CT revealed a tumor in the left maxillary sinus with destruction of the alveolar processes and infiltration of the ethmoid sinus, left orbital cavity, nasal cavity, and subtemporal fossa (Figure 3). The dermatological consultation suggested later in a biopsy the diagnosis of a high-grade diffuse T-cell lymphoma. The left submandibular, axillary, and inguinal lymph nodes were noted to be enlarged during the clinical examination. There were no signs of neoplastic infiltration in the chest and abdomen. In spite of achieved remission with CHOP

Figure 1. T-cell lymphoma: the red-blue colored tumor deformed left maxilla of the patient

Figure 2. T-cell lymphoma: occupation of the mucosa

Figure 3. T-cell lymphoma: the CT revealed the tumor filling the whole left maxillary sinus with destruction of alveolar processes and infiltration of the ethmoid sinus, left orbital cavity, nasal cavity, and subtemporal fossa

Figure 4. T-cell lymphoma: remission after the CHOP chemotherapy and radiotherapy

chemotherapy and radiotherapy (Figure 4), the patient died 10 months later due to the progression of the disease.

Case 4

A 49-year-old white female presented to the clinic with a 3-week history of a painful and inflamed right maxillary process, but in good general condition. The dentist diagnosed the patient with chronic periodontitis, extracted teeth No. 14 and 15, and ordered treatment with clindamycin. However the treatment was unsuccessful and the patient's condition continued to deteriorate. Upon close examination of the oral cavity, inflamed oral mucosa and gross swelling of maxillary alveolar processes were noted. In addition to complaining about paresthesias of the right side of the face supplied by maxillary branch of the trigeminal nerve, the patient also developed annular inflammatory erythematous plaques on the trunk and extremities. During the dermatological consultation, the skin lesions were recognized first to be an allergic reaction to the infection or the drug. On the CT scan, radio-opacity of most of the right maxillary sinus, right nasal cavity, and posterior part of the right pharynx was observed (Figure 5). Subsequent biopsies of the mucosa of the oral cavity only showed nonspecific widespread necrosis and inflammation. On gross examination, granulation tissue was noted on the palate, with necrosis of oral mucosa, palatine tonsil, and of pharyngeal and palatal arches (Figure 6). The third and final histopathological biopsy, performed also after the dermatological consultation, revealed an extranodal NK/T-cell lymphoma,
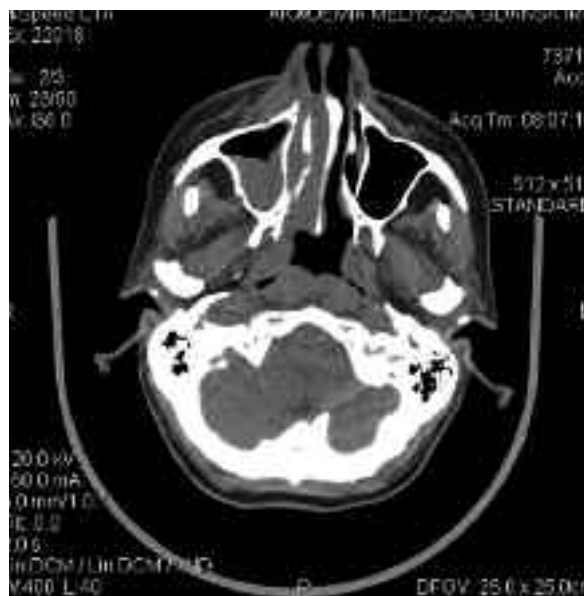

Figure 5. The extranodal NK/T-cell lymphoma, nasal type: the CT revealed opacification of a substantial part of the right maxillary sinus. Also present was a uniform opacity of the right nasal cavity and of the posterior part of the right pharynx, without any apparent osteolytic changes to the bone

nasal type. Despite maximal efforts to save the patient, she developed progression of the disease, circulatory failure and kidney insufficiency and died 6 weeks after initial office presentation.

Case 5

A 16-year-old white female was hospitalized due to a painful tumor of the left maxillary alveolar process causing facial asymmetry (Figure 7). The patient had been treated for chronic maxillary sinusitis for the previous two years. Despite removal of the tooth 4 weeks prior to hospitalization, progressive growth of the tumor continued to be seen. A hemorrhagic tumor was located on the alveolar process surrounding teeth 3-7 (Figure 8). On careful examination of the lymph nodes, left supraclavicular (6 cm) and right submandibular (up to 4 cm) lymph nodes were noted to be enlarged. The CT revealed a tumor of this region (Figure 9), while the biopsy revealed an anaplastic ALK(–) CD30(+) T-cell lymphoma. A complete remission was achieved after chemotherapy, however, the patient was lost during follow up.

Discussion

An epidemic of non-Hodgkin's lymphoma but not other hematopoietic neoplasms has been well documented in many populations [22, 23] with an estimated 50% increase in age-adjusted incidence for the recent few decades of the twentieth century [23-25]. Changes in the diagnostic practice over time and the emergence

Figure 6. The extranodal NK/T-cell lymphoma, nasal type: necrotic lesions covered the entire palate, right maxillary teeth were destabilized

Figure 8. Anaplastic ALK(–) CD30(+) T-cell lymphoma: the hemorrhagic tumor of the alveolar processes surrounding teeth 3-7

Figure 7. Anaplastic ALK(–) CD30(+) T-cell lymphoma: the painful tumor of the left maxillary alveolar
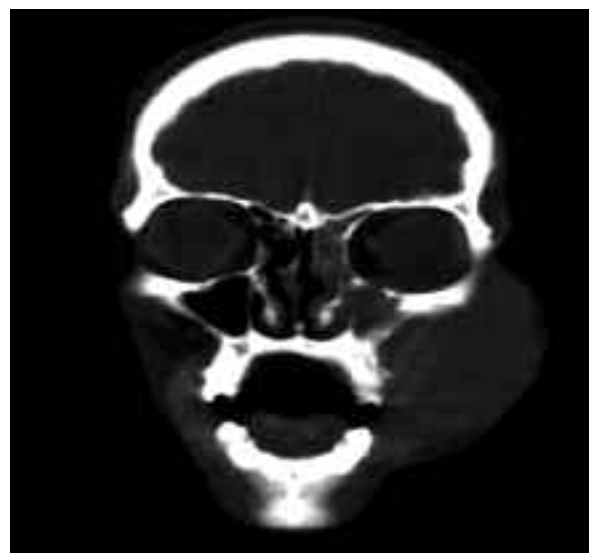

Figure 9. Anaplastic ALK(–) CD30(+) T-cell lymphoma: CT – tumor

of acquired immunodeficiency syndrome (AIDS) pandemic in the early 1980s contributed to the rise of NHL but are not sufficient to explain the dramatic increase in incidence of the lymphomas. The use of immunosuppression including corticosteroids, immunomodulators, and chemotherapy in organ transplant recipients, in connective tissue disorders, but also in the less severe dermatologic diseases like psoriasis or atopic dermatitis, has also influenced the steep rise in incidence of these lymphoproliferative disorders [24, 26-30]. Recent reports suggest that the rise in incidence may have slowed in the late 1990s. Interpretation of NHL rates as a single disease entity requires caution, as the rates reflect a combination of diagnostic and etiologic factors that may differ by each disease subtype [26, 31-33].

Lymphomas arising outside the major lymphoid-bearing sites are termed extranodal (including skin derived subtypes). According to this description, Waldeyer's ring is considered as nodal, but the gastrointestinal tract or upper aerodigestive tract are known as extranodal sites. Primary lymphomas of the upper aerodigestive tract occur most often in the Waldeyer's ring (pharyngeal tonsil, the paired palatine tonsils, lingual tonsils, and tubal tonsils). There is no well-organized mass of lymphoid tissue in the nasal mucosa, but, in chronic sinusitis, well-developed lymphoid follicles can be formed [34].

The head and neck region is one of the most common sites of extranodal NHL with the Waldeyer's ring being the most frequent localization [35-37]. Primary lymphomas arising in the oral cavity are rare and represent less than 10% of cases of lymphomas of the head and neck [38]. The palate appears to be the most frequent localization compared to the maxilla, mandible, gum, oral vestibule and mucosal lip [39, 40]. The tumors arise most frequently in the soft tissues and mucosa, and less often in the bone [41]. Primary lymphomas of the nasal cavity and paranasal sinuses are also uncommon and account for 8-16% of the head and neck lymphomas in the Caucasian population [42, 43]. The maxillary sinus is the most frequently involved structure [44]. It may be clinically impossible to distinguish the origin of the tumor based on the localization of first symptoms. The initial signs and symptoms in all of our patients appeared within the oral cavity, despite the primary tumor being located in the maxilla in few of the cases.

Widespread necrosis and inflammation in the region of the head and neck may frequently be dismissed as a benign or infectious inflammatory process. Thus, by the time a biopsy is taken, the lymphoma may already be in an advanced, incurable stage. A correct and timely diagnosis requires an experienced group of collaborating doctors, including surgeons, dermatologists, laryngologists, internists, and hematologists. Performing numerous biopsies with sufficient amounts of tissue is critical to correctly diagnosing a lymphoma of the head and neck. Pathology laboratories are also obligatory; they should have proper equipment that allows accurate immunocytochemistry of tissues, peripheral blood, and bone marrow. Affected patients will generally present with benign inflammatory changes including rhinitis and chronic periodontitis refractory to antibiotic use. Patients may also present with Wegener's granulomatosis diagnosis itself. The difficulty in the diagnostic process leads to a presentation of an advanced stage of the lymphoma, which then predicts poor prognosis for the patient. As the nature of the disease is one of progressive tissue necrosis, multiple large biopsy specimens are required before sufficient tissue with scattered malignant cells is discovered [45-50]. Careful immunohistochemical assessment is thus vital in order to differentiate these lymphomas from other malignancies as well as benign inflammatory processes.

Most of lymphomas of the head and neck are aggressive B-cell lymphomas like DLBCL (77% of perinasal lymphomas and up to 90% in the oral cavity), followed by indolent lymphomas (MALT type and follicular lymphomas). Burkitt's and Mantle cell lymphomas are rare and account for 5% [43]. In Asian countries, nasal and PNSL lymphomas are more frequent and most of them have NK/T-cell histology [44]. In our case study, there were two B-cell lymphomas and three T-cell lymphomas, including one extranodal NK/T-cell lymphoma, nasal type, which is extremely rare in the European population.

Extranodal lymphomas arising in the head and neck region typically present with non-specific signs and symptoms. The symptoms depend on the aggressiveness of the disease. In indolent lymphomas obstructive symptoms predominate, whereas in aggressive lymphomas, facial swelling, non-healing ulceration, and bone destruction are more prominent [50-53]. Constitutional symptoms are quite uncommon in the initial stages of lymphomas of the head and neck, as was demonstrated by the cases we presented. The lack of constitutional symptoms is one of the reasons why all of these patients were treated initially as having local inflammatory diseases, which is the most frequent pathology seen in this region.

Differential diagnosis of lymphomas of the head and neck includes odontogenic inflammatory processes, periodontal diseases, other malignancies, as well as other benign inflammatory diseases like nonspecific sinusitis, rhinitis, or even Wegener's granulomatosis like our 49-year-old patient with the extranodal NK/T-cell lymphoma, nasal type. The lymphomas may not be recognized earlier due to inadequate tissue obtained for biopsy or insufficient information given to the pathologist by the clinician. Ambiguous results of histopathological tests should signal an alert to the physician of a potential presence of a lymphoma. A study by Yen *et al.* also acknowledged the difficulties in diagnosing sinonasal lymphomas. They pointed out that the presenting symptoms of lymphomas of the head and neck are very similar to benign inflammatory diseases including rhinosinusitis refractory to antibiotic therapy. This group of scientists emphasized

M. Sokołowska-Wojdyło, M. Sikorska, A. Florek, B. Drogoszewska, A. Kowalczyk, A. Starzyńska, A. Szczerkowska-Dobosz, W. Barańska-Rybak, A. Włodarkiewicz

the importance of repetitive biopsies containing sufficient amounts of tissue for histopathological identification. Based on their study, a simple punch biopsy in the nasal cavity did not yield a satisfactory amount of tissue in the majority of the patients. More specifically, advanced surgical techniques were often needed to extract an adequate amount of deep tissue, including partial turbinectomy, Caldwell-Luc, and endoscopic sinus surgery techniques. The fact that sinonasal lymphomas coexist with secondary sinusitis and tend to destroy adjacent anatomic structures, is one of the reasons that contribute to difficulty in harvesting an adequate amount of tissue for biopsy. The study emphasized that clinicians need to be aware that superficial biopsies will often not be enough, as the sinonasal lymphomas frequently have much deeper locations. Patients wait an average of 8.9 months to seek medical help after becoming aware of their symptoms. This late presentation in the office contributes to the advanced stage of lymphoma and thus associated poor prognosis [49].

In spite of the detailed characteristics of the classification of lymphomas updated in 2008 by the Worth Health Organization [21], their diagnosis continues to be challenging, as has been demonstrated by previously outlined cases. Clinicians thus need to have a high index of suspicion of these lymphoproliferative disorders during diagnosis of what may initially appear to be a benign inflammatory process. Extranodal NK/T-cell lymphomas, nasal type, are more often found in the nasal cavities and paranasal sinuses, while the B-cell lymphomas occur more frequently in the palatine tonsils and oral cavity. NHL of the oral or nasal cavity does not have characteristic clinical or radiological symptoms. About half of all NHL cases involve the lymph nodes, yet hematogenous dissemination is also observed. Nasal lymphomas can cause nasal obstruction, rhinorrhea or epistaxis. The ulcerating lesions can cause disfigurement, as the nasal bones are eroded [54]. The first symptoms of the disorder in the oral cavity usually suggest inflammatory disease, for example odontogenic inflammation of maxillary bones, sinusitis or non-lymphoproliferative tumors, such as carcinomas or sarcomas. The erosion of the mucosa on the border of dental prosthesis can also trigger the neoplastic process. Lymphomas are often not painful during the early stages, which often tends to delay their diagnosis. The misdiagnosis may also be caused by inappropriate skin biopsy preservation or by insufficient clinical information presented to the pathologist by the clinician.

The anamnesis and concomitant symptoms should be described in detail. The tissue should be preserved in buffered formalin or sent to the pathologist preserved immediately after the biopsy, which is crucial for performing proper immunohistochemical staining and establishing the correct diagnosis. It is important to recognize the type of lymphoma to choose the appropriate treatment and establish the prognosis. It is very important to differentiate primary lymphomas arising in the oral or nasal cavity from metastasis of other neoplasms to the head and neck region. The prognosis in both cases can be particularly different. Sometimes the process diagnosed initially as a benign inflammation may progress rapidly, and the patient may experience fever, weight loss, and night sweats. And still it is often difficult to recognize the neoplastic process at this stage, especially if the patient was being treated for the past several months for a benign disease. The treatment is often unsuccessful at these late stages, in spite of introducing radiotherapy or chemotherapy. The 5-year survival rate for lymphomas of the head and neck was previously established as 75%, however, it is now known that their recurrence rate is close to 40% [55, 56]. Large cell transformation is clinically significant in some cases of MALT lymphomas and should be documented in histopathological examination. Most importantly, the histopathological subtype of lymphomas has to be correctly established, as it frequently determines the choice of the therapeutic method [57].

In conclusion, the aim of our study was to present the diagnostic difficulties encountered during the diagnosis of lymphomas of the head and neck in dermatological practice. These malignancies often mimic benign inflammatory processes, such as refractory sinusitis or periodontitis, lead to deformities of the face and mucosal lesions, which forces dermatologists to extend the diagnostic process. An accurate diagnosis is often made too late in the disease process, when aggressive chemotherapy and radiotherapy may not be enough to save these patients. Adequate consultations, including dermatological one, and repeated deep tissue biopsies (not punch-biopsies) are often required for a definitive diagnosis, and so is proper tissue biopsy preservation, and thorough clinical information presented to the pathologist by the clinician. Only this will allow for early diagnosis and a potential of saving the life of the patient.

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