HEAD AND NECK LYMPHOMAS – DIAGNOSTIC DIFFICULTIES

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Malignant lymphomas represent approximately 5% of all malignant neoplasm of the head and neck and may involve nodal or extranodal sites. The head and neck region is the second most frequent anatomical site of extranodal lymphomas (after the gastrointestinal tract). Most are non-Hodgkin lymphomas (NHL) of B-cell lineage. Hodgkin’s lymphoma (HL) rarely occurs in extranodal site.

The aim of the study was to evaluate head and neck manifestation of lymphoma (both HL and NHL) and emphasize diagnostic difficulties of these pathologies.

Material and methods. Retrospective review of medical records of patients diagnosed for lymphomas in our department was performed. Authors analyzed demographic data as well as clinical manifestation and diagnostic trials.

Results. 9 patients were included to the study. 7 of them suffered from extranodal NHL and 2 of them from HL (one patient – extranodal and one nodal manifestation). There were diagnostic complications in all cases and final diagnosis was made after surgical material analysis.

Conclusions. This data demonstrate low sensitivity of fine needle aspiration for identification of lymphoma as well as clinical picture is non characteristic.

Key words: lymphoma, head, neck, diagnostics

Lymphatic system neoplasms, which constitute a large and diverse class, often develop in cervical lymph nodes and nasopharyngeal mucosa (1, 2). The currently binding WHO classification of lymphomas distinguishes Hodgkin’s lymphomas, B-cell lymphomas and NK/T-cell lymphomas (non-Hodgkin lymphomas) (3, 4). Lymphomas are second in terms of incidence malignant neoplasms of the head and neck, of which Hodgkin lymphomas constitute 10-35% (2, 5). Hodgkin’s lymphoma occurs usually in young individuals, who most commonly develop this disease in the third decade of life, while the second incidence peak is observed at the age of 65. Males suffer from this neoplasm significantly more often than females (M: F ratio of 1.4: 1.0) (1, 6, 7). The diagnosis of lymphoma in the morphological picture of operating material requires the detection of relevant neoplastic cells (multinucleated Reed-Sternberg (RS) cells and mononuclear Hodgkin cells), elements of inflammatory infiltration and features of fibrosis. The RS cells are usually surrounded by resetting T cells (1, 6, 7, 8). The World Health Organization has adopted the classification into classical Hodgkin’s lymphoma and nodular lymphocyte predominant Hodgkin’s lymphoma (7, 8, 9) (tab. 1).

Most commonly, the first symptom of Hodgkin’s lymphoma is painless enlargement of lymph nodes of the head and neck region. An extranodal form of lymphoma in this area is very rare (< 5%) (9, 10). Approx. 25% of pa-
patients also manifest such general symptoms as weakness, easy fatigability, fever, pruritus, body weight loss and night sweats (1, 6). The prognosis in Hodgkin’s lymphoma is good – a cure rate of 75% may be achieved with modern therapeutic regimens (7). The factor facilitating the development of Hodgkin’s lymphoma is infection with Epstein–Barr virus (1, 5, 8).

As opposed to Hodgkin’s lymphoma, non-Hodgkin lymphomas have extranodal form in as many as 30% of cases, they develop in the head and neck region relatively often, since this is the second in terms of incidence site of such lesions, behind the gastrointestinal tract (9-13). According to Hernsberger, there may be distinguished three types of localisation of non-Hodgkin lymphoma in the head and neck area: 1) intranodal, 2) extranodal, and 3) extranodal extralymphatic. The second category includes Waldeyer’s tonsillar ring lymphomas (15-20% of all lymphomas and almost half of extranodal lesions in the head and neck region), while the third one – lymphomas of the nose, nasopharynx and paranasal sinuses (NHL of upper respiratory tract constitute approx. 5% of all extranodal lesions), oral cavity, mainly base of tongue, salivary glands and skin (11, 12, 14, 15). Head and neck lymphomas usually develop in older individuals (in the six decade of life). The most common symptoms include oedema, pain or discomfort and ulcerations. The majority of non-Hodgkin lymphomas of the head and neck originate from B cells, and the lesions usually represent diffuse large B-cell lymphoma (11, 12). The aetiological factors of primary head and neck lymphomas are not well known, however, their higher incidence in immunosuppressed individuals (particularly in the course of AIDS) and in patients with autoimmune diseases is noted (11, 12, 16, 17). Among the factors facilitating the development of neoplasms in

### Table 1. Classification of Hodgkin Lymphoma according to WHO

<table>
<thead>
<tr>
<th>I. Hodgkin’s lymphoma</th>
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<tbody>
<tr>
<td>1) nodular lymphocyte predominance Hodgkin’s lymphoma,</td>
</tr>
<tr>
<td>2) classical Hodgkin’s lymphoma:</td>
</tr>
<tr>
<td>– nodular sclerosis</td>
</tr>
<tr>
<td>– mixed cellularity</td>
</tr>
<tr>
<td>– classical lymphocyte-rich</td>
</tr>
<tr>
<td>– lymphocyte-depleted</td>
</tr>
</tbody>
</table>

### MATERIAL AND METHODS

Based on the analysis of medical history of patients treated at the Department of Cranial, Oral, Facial and Oncological Surgery in Łódź in the years 2004-2009, a group of 9 patients was selected with diagnosed head and neck lymphoma based on the post-operative material. There were analysed demographic and clinical data, and discussed in detail the diagnostic problems encountered in the above patients, preventing primary systemic treatment, individualised for the given disease entity, at the oncology centre.

### RESULTS

Within the past 5 years, there were 9 patients with viscerocranial lymphomas treated at the Department of Cranial, Oral, Facial and Oncological Surgery in Łódź (tab. 2). 6 patients were diagnosed with B-cell non-Hodgkin lymphoma, 1 patient – with extranodal Hodgkin’s lymphoma and 1 patient – with nodal Hodgkin lymphoma. The patient age ranged between 50 and 84. Females predominated (tab. 3). In patients with diagnosed non-Hodgkin lymphoma, the disease history was relatively short (approx. 3 months in all of them). Patients reported the appearance of a rapidly growing painless lump. Patients did not report any additional symptoms, such as weakness, subfebrile states or night sweats. In none of the patients the results of fine-needle aspiration biopsy (FNAB) revealed lymphatic tissue proliferation or malignancy, therefore, initially, the patients were not qualified for systemic treatment but for tumour resection. The only exception was 1 female patient in whom the

### Table 2.

<table>
<thead>
<tr>
<th>Lymphomas</th>
<th>No of patients</th>
</tr>
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<tbody>
<tr>
<td>B-cell NHL, extranodal</td>
<td>7</td>
</tr>
<tr>
<td>HL, extranodal</td>
<td>1</td>
</tr>
<tr>
<td>HL, nodal</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
</tr>
</tbody>
</table>
Head and neck lymphomas – diagnostic difficulties

Result of microscopic examination of tumour specimen stated: malignant neoplasm, poorly differentiated, with necrotic foci, most likely G3 adenocarcinoma. The patient underwent a viscerocranial CT scan, which revealed an osteolytic loss in the region of alveolar recess of the left maxillary sinus. In the recess, there was visualised a solid infiltration involving the soft palate and the left lateral and posterior nasopharyngeal walls. The radiologist interpreting the examination results suggested that the picture indicated proliferation. In addition, there was observed the presence of a lymph node bundle in the region of left angle of the mandible. In ultrasound examination, there was also found irregular, thick-walled lesion in the left parotid gland, of 3 cm in diameter.

In view of the above, partial left maxillectomy and salivary gland tumour resection were performed, as well as omosuprahyoid lymphadenectomy and non-radical nasopharyngeal tumour resection. The procedure was aimed at maximum reduction in the tumour mass for the purposes of adjuvant combination treatment with chemotherapy and radiation therapy. However, the examination of operating material indicated B-cell non-Hodgkin lymphoma (immunohistochemistry: LCA (+++), CD20 (+++), CD3 (+) in isolated tumour cells, cytokeratin (-). The patient received systemic treatment at the oncology centre. In two patients, multiple parotid gland tumours were found. In one of the above patients, a female aged 84, microscopy and immunohistochemistry on the operating material revealed: visualised structure of a tumour comprising round cells with small cytoplasm and extensive nuclear polymorphism, not forming organoid structures. The neoplasm has necrotic zones and infiltrates the skeletal striated muscles; LCA – positive in all tumour cells, CD20 – positive in all tumour cells, cytokeratin – negative in tumour cells, Ki-67 labelling index – 70% immunopositive nuclei. The microscopic picture and immunohistochemistry results indicate lymphoma malignum typus MALT large cell B. In another patient, a female aged 66, there was determined by immunohistochemistry CD20 (+++) in the majority of neoplastic cells and CD3 (+) in some of them.

Significant diagnostic problems were also encountered in a female patient aged 50 who reported to the centre due to left cheek oedema. Based on multiple aspiration biopsies, the ultimate diagnosis was not possible. There were considered, among others: T-cell lymphoma and carcinoma planoepitheliale. Cervical and submandibular ultrasound examination was performed, revealing extensive infiltration by a hypoechogenic solid (and potentially partially liquid) structure. The lesion infiltrated subcutaneous tissue and muscular structures, clearly extending to the masseter muscle. The mandibular bone outline was irregular, with losses. In the left submandibular region, there was found the presence of several enlarged lymph nodes of 15 mm, with atypical, yet probably not inflammatory, characteristics. The lesion did not exhibit contact with salivary glands. A decision was made on performing bone scintigraphy of viscerocranium (HEDP 625 MBg). The interpretation of three-phase examination results was as follows:

Phase 1 – perfusion of tissues in the left mandibular region is clearly increased;
Phase 2 – the blood pool in tissues surrounding the left mandible is increased;
Phase 3 – the bone metabolism is increased.

<table>
<thead>
<tr>
<th>No</th>
<th>Diagnosis</th>
<th>Age</th>
<th>Gender</th>
<th>Localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>HL</td>
<td>50</td>
<td>F</td>
<td>left cheek</td>
</tr>
<tr>
<td>2.</td>
<td>HL typu NS</td>
<td>54</td>
<td>F</td>
<td>right submandibular lymph node</td>
</tr>
<tr>
<td>3.</td>
<td>B-cell NHL (MALT)</td>
<td>84</td>
<td>F</td>
<td>right parotid gland</td>
</tr>
<tr>
<td>4.</td>
<td>B-cell NHL</td>
<td>66</td>
<td>F</td>
<td>left parotid gland</td>
</tr>
<tr>
<td>5.</td>
<td>B-cell NHL</td>
<td>51</td>
<td>F</td>
<td>right parotid gland</td>
</tr>
<tr>
<td>6.</td>
<td>B-cell NHL</td>
<td>69</td>
<td>F</td>
<td>right parotid gland</td>
</tr>
<tr>
<td>7.</td>
<td>B-cell NHL</td>
<td>62</td>
<td>F</td>
<td>alveolar recess of maxillary sinus, soft palate, nasopharynx, left cheek, submandibular lymph nodes</td>
</tr>
<tr>
<td>8.</td>
<td>B-cell NHL</td>
<td>74</td>
<td>M</td>
<td>right lateral tongue surface</td>
</tr>
<tr>
<td>9.</td>
<td>B-cell NHL (MALT)</td>
<td>54</td>
<td>M</td>
<td>submandibular gland, right submandibular space</td>
</tr>
</tbody>
</table>
Phase 3 – marker accumulation in the left mandible is clearly increased.

In addition, slightly increased marker accumulation in the right mandible is observed. No focal lesions were found in the remaining bone tissue. It was decided to collect a specimen from the mandibular lesion, which provided a reliable microscopy result as follows: the microscopic picture, as well as the performed immunohistochemical tests (CD1a, CD3, CD15, CD20, CD30, CD68, LCA, EMA, ALK-1, VIM) and auxiliary immunohistochemical tests (CD3, CD34, UCHL1 oraz Nk1) allow to rule out the diagnosis of T-cell lymphoma. The RS cell phenotype corresponds to Hodgkin’s lymphoma. The female patient with an extremely rare form of extranodal extralymphatic Hodgkin’s lymphoma received systemic treatment at the oncology centre.

DISCUSSION

The studied group of patients comprised individuals aged above 50, with the disease being diagnosed in the sixth decade of life, which is in agreement with the global epidemiological data (1, 3, 9, 18, 19). In over half of the patients, lymphoma developed in the salivary gland. This localisation is second in terms of frequency extranodal site of this neoplasm in the head and neck region, behind tonsils (18, 20). NHL of salivary glands, similarly as in the presented material, affects most commonly parotid glands (up to 80% of cases), followed by submandibular glands (16%), sublingual glands (2%) and minor salivary glands (2%) (14). This neoplasm is most often diagnosed in females (with male-to-female ratio of 1:2), which is also observed in the studied group (14).

In all patients with diagnosed NHL, it was B-cell lymphoma. This is the most common form of non-Hodgkin lymphoma in the head and neck region (1, 3, 11, 12, 18, 20, 21). Among the above patients, two were diagnosed with MALT lymphoma. This is a neoplasm often characterised by localised form, slow progression and many-year history – as was the case of patients described in the present report (2 years in a female patient aged 84, and 3 years in a male patient aged 54). This often causes diagnostic errors due to the presence of concomitant inflammation (14, 19). In their diagnosis, molecular biology and determination of one of the four translocations usually observed in MALT lymphoma cells, namely t(11;18) (q21;q21), t(14;18)(q32;q21), t(3;14)(p14.1;q32) or t(1;14)(p22;q32), may be useful (14, 19). It is also of significance that the treatment of choice might be simple resection and external beam radiation therapy. However, of note is the higher incidence of recurrence and disease dissemination following such a treatment (14, 19).

International reports emphasise higher lymphoma incidence in patients with diagnosed autoimmune disorders (11, 12, 17, 19). In the group of studied patients, there was found only one case with positive history for this – a male aged 54 with NHL MALT. The above patient had been treated for Grave’s disease. Of note is the concomitant occurrence of pathological mass in the right submandibular region and ophthalmological symptoms. The long-term lymphoma history also covered a reduction in the cervical pathological mass following the administration of steroid bolus injections, which additionally extended the time needed for diagnosis (reduction in patient anxiety and reluctance to report to the physician for lump diagnosis). In all patients included in the present study, there occurred initial diagnostic problems at the stage of interpretation of fine-needle biopsy results. Roh and Long and colleagues have previously investigated the diagnostic microscopy problem in head and neck tumours that proved lymphomas. The former studied a group of 173 patients of which 109 had undergone more than one fine-needle biopsy prior to lymphoma diagnosis, while the latter analysed the diagnostic approach in 117 patients. In both reports the FNAB sensitivity was approx. 60%. The authors also noted the statistically significant delay in diagnosis in multiple biopsy cases as compared with excisional biopsy in patients with high risk of lymphoma development (22, 23). The increase in sensitivity of fine-needle biopsy in patients with diagnostic problems post clinical examination, imaging diagnostics and initial histological diagnostics (first fine-needle biopsy) may be achieved by phenotyping with the use of flow cytometry on the biopsy specimen and preliminary immunohistochemistry. However, it is still an imperfect tool and the only reliable results are provided by tissue examination preceded by excisional biopsy (22, 23, 24).
CONCLUSIONS

It is definitely stated that lymphomas should be diagnosed based solely on the histopathological assessment of material collected during surgery and not on the clinical picture and fine-needle biopsy results. In the diagnostics of head and neck lymphomas, the sensitivity of fine-needle biopsy is not sufficient. The clinical symptoms are not characteristic and may cause initial diagnostic errors, which in consequence lead to the extension of time needed for initiating proper systemic treatment.

REFERENCES