RESEARCH ARTICLE

Diagnostic Challenges of Lymphoblastic Lymphomas of the Mediastinum

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Abstract: Background: Lymphoblastic lymphomas (LL) of the mediastinum are rare tumours that present a challenging diagnosis. The positive diagnosis is based on microscopic findings. Our aim was to highlight the diagnostic difficulties in such situations.

Methods: We conducted a descriptive retrospective study including 31 patients presenting mediastinal LL.

Results: Radiologic features consisted in all cases in a mediastinal infiltrating mass. Microscopic examination showed in all cases a crowded tumour with many artefacts made of diffuse tumour cells. Immunohistochemical study was performed in all cases. It was quite difficult to interpret in the samples used for extemporaneous examination and repeated in 10 cases.

Conclusion: The diagnosis of LL is based on the microscopic examination which is usually performed on small samples with crowding artefacts. Thus, this pathology must be managed by a trained team that is used to deal with such a specimen in order to avoid repeating the biopsy and inducing diagnostic delay.

Keywords: Diagnosis, lymphoblastic lymphoma, pathology, T-cell lymphoma, pathology, mediastinum.

1. INTRODUCTION

Primary mediastinal lymphomas account for less than 10% of all lymphomas. They are mainly represented by Hodgkin’s lymphoma, diffuse large B cell lymphoma and lymphoblastic lymphomas (LL). The latter are rare tumours accounting for less than 2% of non-Hodgkin lymphomas. The majority of them are T-cell-types and approximately 10 to 15% are precursor B-cell lymphomas [1-3]. It is a diagnostic and therapeutic emergency. In a survival study about LL of the mediastinum, Mlika, et al reported a global survival of 85% at 8 months and 70% at 12 months and a mean survival of 24 months [4]. A positive diagnosis is based on microscopic examination, which is usually performed on a small specimen with crowding artefacts. This fact is due to the difficulty of complete resection of these tumours. They are classified as T lymphoblastic lymphoma in 85 to 90% of the cases [5-7].

Our aim was to describe the epidemiological, the clinical, the radiological and the diagnostic features of these tumours through a 16-year-experience of a single institution.

2. MATERIAL AND METHODS

2.1. Patients

We report a descriptive retrospective study about 31 lymphoblastic lymphomas diagnosed over a 16-year-period in our Pathology Department and managed in the Hematology Department.

All the LL diagnosed from 2000 to 2015 were included in our study. The different reports were recorded in our Department of pathology.

Mediastinal tumours that were not classified as lymphoblastic lymphoma weren’t included in our study.

The patients without clinical databases were excluded.

2.2. Methods

The clinical records of the patients were recorded. The items included were age, sex, symptoms, radiological features, extension examination and therapeutic management. The follow-up period extended from the onset of the clinical history to January 2016. All the slides were reviewed by 2 pathologists (MM, FM). The nature of the specimen, the gross examination, the microscopic features and the crowding artefacts were recorded.
The immunohistochemical study was performed in all cases using a manual method performed by the same technician. The different antibodies used were: CD3, CD5, CD99, CD1a, CD45, Tdt, Ki-67, CD20, CK, EMA, CD79a, CD15 and CD30 antibodies. Table 1 represents the different clones and dilutions of antibodies.

2.3. Statistical Analysis

The statistical analysis was performed using the SPSS software (version 15.0).

2.4. Ethical Considerations

Consent was obtained from all patients or parents for the children’s parents.

2.5. Bibliographic Research

Bibliographic research was performed using the Pubmed, Google scholar and Science Direct sites using these keywords: lymphoblastic lymphoma, mediastinal lymphoma.

3. RESULTS

During the period of the study, 1500 mediastinal tumours were diagnosed in our department and 31 tumours were classified as LL. These tumours accounted for 2% of the mediastinal tumours assessed in our department. Four patients presented a particular past medical history characterized by high blood pressure in 2 cases, diabetes mellitus in 1 case 77 and asthma in 1 case.

The median delay of consultation was 6 weeks (average, 2 to 44 weeks). The mean time used to work-up for giving a definite diagnosis was 7 days (average, 3 to 15 days).

Physical examination was normal in 2 patients. In the other patients, it revealed cervical, supraclavicular, axillary lymph nodes in 12 patients (39%), superior vena cava syndrome in 9 patients (29%), hepatomegaly in 3 patients, splenomegaly in 1 patient (13%) and a decrease of the vesicular murmur in 18 patients.

Laboratory investigations were within normal values in 10 cases and abnormal in 19 patients. They weren’t recorded in other cases. The abnormalities consisted of hyperleucocytosis in 18 patients, severe anaemia in 1 patient, hyperuricemia and hyperphosphatemia in 1 patient and mixed alkalosis in 2 patients.

The chest-x-ray revealed a homogeneous mediastinal mass in 25 patients associated to a pleural effusion in 26 patients and a pericardiac fluid in 2 cases, an isolated pleural effusion in 6 patients and a mediastinal enlargement associated to a left lung mass in 5 patients and a white left lung in 1 patient (Fig. 1).

The chest-CT-scan showed a mediastinal mass with a mean size of 13 cm. The mediastinal mass was associated with pleural effusion in 26 cases, a venous compression in 8 cases, pericardial effusion in 5 cases (Fig. 2).

The abdominal CT-scan was abnormal in 11 patients. It showed hepatomegaly in 6 cases, splenomegaly in 3 cases, retroperitoneal lymph nodes in 4 cases, a multinodular renal mass in 2 cases, an ovarian mass in 1 case and a nodular testicular mass in 1 case. Bone marrow biopsy was performed in 21 patients. It was infiltrated in 7 cases. Pleural fluid was metastatic in 1 case. Twenty-five patients presented a disseminated involvement of one or more extralymphatic organ and nodal involvement. Those patients were included into a stage IV group according to the Ann Arbor classification. Table 2 illustrates the patients’ characteristics.

The diagnosis was performed in all cases on biopsies including pleural biopsy in 8 cases, VATS mediastinal biopsy in 14 cases, lymph node biopsy in 8 cases and tracheal biopsy in 1 case. The biopsy was repeated in no
Fig. (1). Chest-X-ray showing a mediastinal enlargement (arrow) with a left pleural effusion (double arrow).

Fig. (2). CT-scan showing a huge mediastinal mass (arrow) associated to a left pleural effusion (double arrow).

case. The extemporaneous examination consisted of the assessment of frozen sections. It was performed in 18 cases and concluded to an undifferentiated malignant process in all cases. The samples received were crowded, small with a mean size of 1 cm.

Microscopic examination showed in all cases a crowded tumour with many artefacts made of diffuse tumour cells. The latter were small to medium with basophilic cytoplasm. The nuclei were rounded, with irregular contours usually nucleolated. Many mitotic figures were noticed (Fig. 3a-c).

An immunohistochemical study was performed in all cases. It was quite difficult to interpret in the samples used for extemporaneous examination and repeated in 10 cases. The difficulties encountered in the interpretation of the immunohistochemical study were due to the deterioration of the antigenic determinants of the tumour cells dealing with false negative cases. Touch imprints can be useful in order to minimize the samples during the extemporaneous examination but can’t be used alone to make the diagnosis.

It showed the positivity of the tumour cells with the CD3 and CD5 antibodies in all cases. It showed the positivity of the CD99 in 22 cases, CD1a in 15 cases, Tdt in 21 cases and ki-67 in all cases. The CD20 antibody was negative in all cases in addition to the CD15 and CD30 antibodies (Fig. 3d-f). All the tumours were negative with the CD45, CK, EMA and CD79a antibodies.

Two patients died before the onset of the treatment. Twenty-nine patients received a chemotherapy according to
Table 2. Patients’ characteristics.

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Chest-x-ray</th>
<th>CT-scan</th>
<th>Abd CT-scan</th>
<th>BMB</th>
<th>LP</th>
<th>Stage</th>
<th>Biopsy</th>
<th>TT</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>M</td>
<td>Cough</td>
<td>Mediastinal</td>
<td>MM+ pleural effusion</td>
<td>Liver, splenic Enlarg</td>
<td>Inf</td>
<td>NI</td>
<td>IV</td>
<td>Pleura</td>
<td>GRALL03</td>
<td>Death</td>
</tr>
<tr>
<td>38</td>
<td>M</td>
<td>Dyspnea + cough + CP</td>
<td>Mediastinal</td>
<td>MM+ pleural effusion + venous compression</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>IV</td>
<td>Pleura</td>
<td>GRALL03</td>
<td>Aplasia</td>
</tr>
<tr>
<td>8</td>
<td>W</td>
<td>Dyspnea + CP</td>
<td>Mediastinal</td>
<td>MM+ pleural effusion</td>
<td>NI</td>
<td>Inf</td>
<td>NI</td>
<td>IV</td>
<td>Mediastinum</td>
<td>EORTC</td>
<td>Aplasia</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>CP+ Cervical lymph nodes</td>
<td>Mediastinal</td>
<td>MM+ pleural effusion and pericardiac fluid</td>
<td>NI</td>
<td>LN</td>
<td>CHOP</td>
<td>No response</td>
<td>LOV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>M</td>
<td>Dyspnea</td>
<td>Mediastinal</td>
<td>MM</td>
<td>NI</td>
<td>Inf</td>
<td>NI</td>
<td>III</td>
<td>Pleura</td>
<td>EORTC</td>
<td>Aplasia</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>Dyspnea + CP</td>
<td>Pleural fluid</td>
<td>MM+ pleural effusion</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>III</td>
<td>Pleura</td>
<td>EORTC</td>
<td>Aplasia</td>
</tr>
<tr>
<td>16</td>
<td>W</td>
<td>Dyspnea + CP + Cervical LN</td>
<td>Pleural fluid</td>
<td>MM</td>
<td>Liver, Enlarg</td>
<td>Inf</td>
<td>NI</td>
<td>IV</td>
<td>LN</td>
<td>EORTC</td>
<td>Aplasia, cerebral phlebitis, Death</td>
</tr>
<tr>
<td>16</td>
<td>W</td>
<td>Dyspnea</td>
<td>Pleural fluid</td>
<td>MM+ pleural effusion</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>III</td>
<td>Mediastinum</td>
<td>EORTC</td>
<td>Diabetes, fever</td>
</tr>
<tr>
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<td>MM+ pleural effusion + pericardiac fluid</td>
<td>Ovarian mass</td>
<td>NI</td>
<td>NI</td>
<td>IV</td>
<td>Pleura</td>
<td>EROTC</td>
<td>LOV</td>
</tr>
<tr>
<td>22</td>
<td>M</td>
<td>Dyspnea + cough</td>
<td>MM</td>
<td>MM+ pleural effusion + abdominal LN</td>
<td>Nl</td>
<td>Ni</td>
<td>Ni</td>
<td>IV</td>
<td>LN</td>
<td>EORC</td>
<td>aplasia, GGS</td>
</tr>
<tr>
<td>22</td>
<td>M</td>
<td>Dyspnea + CP + fever</td>
<td>MM</td>
<td>MM+ Pericardiac fluid</td>
<td>Trachea CT</td>
<td>CT</td>
<td>GGS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>W</td>
<td>cough</td>
<td>MM+ pleural effusion</td>
<td>MM+ pleural effusion</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>IV</td>
<td>Mediastinum</td>
<td>Hyper-CVAD</td>
<td>Death</td>
</tr>
<tr>
<td>26</td>
<td>M</td>
<td>Dyspnea</td>
<td>Pleural effusion</td>
<td>MM+ Pleural effusion + Pericardiac fluid + Venous compression</td>
<td>Mesenteric LN</td>
<td>Inf</td>
<td>Inf</td>
<td>IV</td>
<td>Mediastinum</td>
<td>EROTC</td>
<td>Hepatic cytolysis GGS</td>
</tr>
<tr>
<td>29</td>
<td>M</td>
<td>Dyspnea</td>
<td>MM</td>
<td>MM+ Pleural effusion + Mesenteric LN</td>
<td>Ni</td>
<td>Ni</td>
<td>Ni</td>
<td>II</td>
<td>LN</td>
<td>GRALL03</td>
<td>LOV</td>
</tr>
</tbody>
</table>

Fig. (3). (a) Gross features of the samples obtained through mediastinoscopy, (b) microscopic features showing a diffuse malignant proliferation with crowding artefacts (HE x 200), (c) microscopic features showing many tumour cells with atypical nuclei that are difficult to analyse (HE x 400), (d) immunohistochemical study showing the diffuse cytoplasmic expression of CD3 by tumour cells, (e) immunohistochemical study showing the diffuse nuclear expression of Tdt by the tumour cells, (f) immunohistochemical study showing the expression of Ki-67 by about 80% of the tumour cells (HE x 400).

the following protocols: EORTC in 12 cases (Dexamethasone - L-Asparaginase-Cyclophosphamide - Methotrexate), GRAALL003 in 8 cases (Prednisone- Doxorubicine - Cyclophosphamide-Vincristine- L-Asparaginase), CHOP in 1 case (Cyclophosphamide - Vincristine - Doxorubicine - Dexamethasone), CHOP modified in 1 case (association de Rubido qui est hors protocole), HYPER-CVAD in 1 case (Cyclophosphamide - Vincristine - Doxorubicine - Dexamethasone - Methotrexate - Cytarabine).

Four patients received preventive radiation therapy. An allograft was possible in 1 case. During the follow-up period, 24 patients presented complications. These complications were infectious in 12 patients, metabolic in 8 patients, hematologic in 16 patients, neurologic in 4 patients. The response to the induction treatment was available in 8 patients. 2 patients died immediately after the biopsy. One patient died during the induction treatment. One patient has been receiving chemotherapy. Four patients were lost of view.

The global survival was estimated to 85% at 8 months and 70% at 12 months with a mean survival of 24 months.

4. DISCUSSION

Lymphoblastic lymphoma of the mediastinum is mainly of T phenotype (85 -90% of the cases) [8]. This tumour is mainly observed in children and young adults. The mean age of the patients included in our study was 26 years. The male predominance was observed either in this study or in the literature. Risk factors of these lymphomas aren’t clearly established [9, 10]. In our study, the past medical history of our patients didn’t point out a particular predisposing factor. Respiratory symptoms are the most frequent symptoms and 71% of our patients presented respiratory symptoms. Physical examination is usually abnormal and it revealed in 40% of our patient's peripheral lymph nodes. Besides, 29% of our patients presented a compression vena cava syndrom.

Chest-x-ray shows non-specific signs. Chest-CT-scan plays a key role in order to assess the diagnosis and to highlight the extension to the contiguous organs. In our study, it showed in almost all cases mediastinal masses with pleural fluid. The pet-scan plays a key role in diagnosing and staging these diseases [11]. It wasn’t performed in our study because of its cost, especially in a low-income country.

Microscopic examination was performed in all cases on biopsies and extemporaneous examination was performed in all mediastinal biopsies. This examination was not performed in the literature. Its utility consists in the estimation of the diagnostic availability of the specimen that was sent. The samples received were small varying from 1 cm to 2.5 cm. The extemporaneous examination induced difficulties of the interpretation of the immunohistochemistry results and compelled the pathologists to repeat the assessment of the expression of many antibodies. In all cases, a diffuse lymphomatous proliferation with many artefacts was observed. Tumour cells were round or oval with granular chromatin and numerous figures of mitoses. The immunohistochemical study was performed in all cases using the CD3, CD1a, CD2, CD4, CD5, and Tdt antibodies [9]. The artefacts can induce difficulties of interpretation. The major differential diagnosis is represented by type B1 thymoma. In fact, the diagnostic features of thymomas which are the lobulation and the co-existence of epithelial cells and immature lymphocytes may not exist dealing with some difficulties. In case of absence of these diagnostic features, the correlation with the radiologic findings may highlight the diagnosis because B1 thymomas are generally well limited. During the period of the study, 15 cases of B1 thymomas were recorded in our Department. This fact highlights the importance of ruling out this diagnosis.

The majority of the patients presented a stage IV disease. The treatment is based on chemotherapy regimens. In our study, 2 protocols were widely used including EORCT and AALL03 in children and CHOP and the Hyper-CVAD in
CONCLUSION

The lymphoblastic lymphoma of the mediastinum is a rare disease affecting mainly children and young adults of male sex and is mainly revealed by respiratory symptoms. The positive diagnosis is based on the microscopic features. It is usually made on small samples with many artefacts. In our study, the small size of the specimen and the damages induced by the extemporaneous examination dealt with challenging immunohistochemical studies but no biopsy needed to be repeated. This fact can be explained by the degree of training of the pathologists. Avoiding diagnostic delay is a major goal in order to start the chemotherapy regimens as soon as possible [10].

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

It has been obtained from the committee of Ethics of the Faculty of Medicine of Tunis.

HUMAN AND ANIMAL RIGHTS

No Animals were used for studies that are base of this research. All human procedures were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

Human subjects used in the study provided informed consent to participate.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

This research work was performed within the activity of the research laboratory: LR18SP06

REFERENCES