Rare thymic malignancy of B-cell origin – T-cell/histiocyte-rich large B-cell lymphoma

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Abstract

Aim: T-cell/histiocyte-rich B-cell lymphoma is a rare type of diffuse large B-cell lymphoma reported as involving primarily the thymus only by one paper in the English literature. Case presentation: A four and a half years old boy was admitted, after a sudden onset in the middle of the night, with superior vena cava syndrome, resuscitated cardiac and respiratory arrest and severe coma with Glasgow Coma Scale rate of 3. In spite of intensive treatment, the patient repeated twice the cardiac arrest and died sixteen hours after admittance. The autopsy confirmed the existence of a huge mediastinal mass, revealed by the prior to death computed tomography examination, and the thorough histopathological established the diagnosis of T-cell/histiocyte-rich large B-cell lymphoma of the thymus with renal spread. Discussion: The particularities of the presented case are the primary location of the lesion in the thymus, the age of the patient, very young, the lack of lymph nodes involvement and the rapid development of the disease until death without any possibility of therapeutic specific intervention. Conclusions: The case is the second reported in the literature with primary involvement of the thymus by this rare variant of diffuse large B-cell lymphoma. The histopathological examination is the golden standard for the diagnosis. Any clinical symptom of unexplained fatigue and dyspnea in a child should raise the clinician’s suspicion of a mediastinal mass involving the thymus.

Keywords: thymus, lymphoma, T-cell/histiocyte-rich large B-cell lymphoma.

Introduction

The thymus is one of the primary lymphatic organs and the primary anatomic site of T-cell development [1–3]. However, many studies pointed out throughout time the presence of a reduced contingent of B-cells in the human thymic parenchyma [4–7]. Therefore, although the majority of lymphoid thymic malignancies have T-cell lineage, with T-cell lymphoblastic lymphoma (TCLL) the most frequent, followed by Hodgkin’s lymphoma (HL), lymphoid malignancies of B-cell origin and especially primary mediastinal large B-cell lymphoma (PMBCL), are not a rare presence, even within the thymus [1, 3, 8–10]. T-cell/histiocyte-rich large B-cell lymphoma (TC/HRLBCL) is recently recognized, rare morphological variant of diffuse large B-cell lymphoma (DLBCL), accounting for less than 2% of all DLBCLs 1% to 3% of all B-cell lymphomas [3, 11–14]. Ramsay et al. signaled it in the late ’80s, and Delabie et al. identified it four years later as a distinct subgroup, and named it “histiocyte-rich B-cell lymphoma” [15, 16]. World Health Organization (WHO) recognized it as a distinct pathological entity for the first time in 2001 and included it as a specific subtype of DLBCL in its 2008 Classification, together with primary DLBCL of the central nervous system (CNS), primary cutaneous DLBCL, leg type, Epstein–Barr virus (EBV)þ DLBCL no other specified (NOS) and (EBV)þ mucocutaneous ulcer, the last two entities being modified and introduced in the latest revision of the WHO classification of lymphoid neoplasms [17–19].

In 2016, Xu et al. report a case that they state to be the first TC/HRLBCL with thymic location [3].

We report in this paper another case of thymic TC/HRLBCL, discovered during routine autopsy of a small child, deceased not long after admission.

Case presentation

Clinical assessment

A four years and six months old boy was admitted in the Intensive Care Unit (ICU) of the Emergency County Hospital of Craiova, Romania, at around 2:00 o’clock in the night, with coma and resuscitated cardiac and respiratory arrest at home by the ambulance team.

The young patient, without significant personal pathological history, was complaining from several weeks of moderate effort fatigue. The disease had an acute onset, at home, in the middle of the night, the patient being woken up suddenly by severe dyspnea with orthopnea, followed rapidly by cardiac and respiratory arrest. The ambulance team requested manages to resuscitate the patient and brings him to the Hospital, where he was admitted in the ICU.
The clinical examination in the ICU revealed an afebrile and of normal weight patient with severe general state, comatose, with gasping and mydriatic non-reactive pupils, intubated and mechanically ventilated. The facial and upper extremities edema was present, the abdomen was relaxed and the diuresis was absent. The pulse rate was of 140 beats/min and the blood pressure was of 136/97 mmHg.

Emergency laboratory tests revealed only metabolic acidosis, the other biologic investigations having normal values.

Cardiac and abdominal ultrasound examination showed a rim of pericardial fluid in Morrison space who surrounds the splenic upper pole.

With a first diagnosis of superior vena cava syndrome, postanoxic coma and cardiac and respiratory resuscitated arrest, an urgent computed tomography (CT) is requested.

**CT assessment**

The skull examination revealed the effacement of cortical sulci of both supra and infratentorial regions, bilaterally, with lateral ventricles placed medially and with reduced dimensions, suggesting diffuse cerebral edema.

The thoracic examination revealed a bulky mediastinal mass of around 13.5 cm, with significant iodophilia who surrounds and compresses mediastinal vascular structures, the heart, the trachea and principal bronchi and produces right pulmonary collapse and iodophil condensation of left inferior lobe, suggesting pulmonary atelectasis (Figure 1, a–c and g). The right pleural cavity contained pleural fluid.

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**Figure 1 – CT and necropsy features of the mediastinal tumor:**
(a) Anterior part of the mediastinum with the largest diameters of the tumor; (b) Posterior part of the mediastinum, with tumor embedding mediastinal vascular structures and producing right pulmonary collapse; (c) Tumor compresses the heart and embeds mediastinal vascular structures; (d) Anterior aspect of the tumor, encapsulated; (e) Posterior aspect, with fibrous pericardium not invaded; (f) Cut surface of the tumor with whitish, lobulated appearance. A: Anterior; P: Posterior; L: Left; R: Right.
There was fluid in the peritoneal cavity also. The liver and the spleen were enlarged with narrowing of vascular structures and homogenously reduced iodophilia. Pancreas had no located processes. The kidneys showed homogenous, reduced nephrogram bilaterally. The abdominal aorta had 0.7 cm in diameter.

**Outcome**

Despite the intensive treatment set up, the patient has two more cardiac and respiratory arrests that are resuscitated but, in the end, dies at the third cardiac arrest, after 16 hours from the admission.

Following the legal procedures, the autopsy was requested.

**Autopsy**

The abnormal aspects revealed by the autopsy were:

- Presence of fluid in pleural cavity bilaterally, in a total amount of 300 mL.
- Huge tumoral mass placed in the anterior mediastinum, measuring 14/10/4.5 cm, which seemed encapsulated and “embedded” the main vascular trunks of the aortic cross. The cut surface had a fatty lobulated aspect, with few hemorrhagic foci (Figure 1, d–f and h). There was no gross sign of pleural or pericardial invasion (Figure 2, a–d).
- Presence of fluid in small quantity in peritoneal cavity.
- Liver with hepatomegaly (19/16/9 cm) but with a normal aspect of external and cut surfaces.
- Spleen with splenomegaly (10/7/3 cm) but with a normal aspect of external and cut surfaces.
- Kidneys had normal dimensions for the age but presented, on the cut surface, whitish nodules of variable dimensions, placed in the cortical areas bilaterally.

![Figure 2 – Local extension. Tumor mass is encapsulated but does not invade pleura and pericardium (a–d); Cellular proliferation invades tumor capsule but not the parietal pleura (e and f) and the fibrous pericardium (g and h), HE staining, ×100. A: Anterior; P: Posterior; L: Left; R: Right.](image-url)
Histopathological assessment

The tumor mass was surrounded by a fibrous capsule who was in apposition with the parietal pleura (Figure 2, e and f) and the fibrous pericardium (Figure 2, g and h).

The thymic architecture was effaced, with no obvious borders between cortical and medullar areas of the lobules, by diffuse proliferation of T-cells with a CD3+/CD5+ profile which were either CD4+ or CD8+, the latter being slightly predominant (Figure 3, left; Figure 4) with focally scattered nodular agglomerations of CD20+ B-cells (Figure 3, left; Figure 5).

The characteristic epithelial network was also disrupted as AE1/AE3 immunostaining revealed, and only rare Hassall’s corpuscles were observed (Figure 3, right).

The background of lymphocytic proliferation contained some scattered non-epithelioid CD68+ histiocytes but no follicular dendritic cells (immunomarking for CD23 was negative) (Figure 4).

The hyperplastic lymphoid infiltrate invaded the tumoral capsule but did not exceed it into the parietal pleura (Figure 2, e and f) and the fibrous pericardium (Figure 2, g and h).

In this cellular background of abundant T-cells, a small number of large, atypical B-cells with irregular nuclei, vesicular chromatin, and one or more nucleoli were scattered in the effaced areas, amid the nodular agglomerations of CD20+ B-cells.

A panel of seven antibodies was used for the identification of these atypical B-cells with the following results: positivity for CD20, CD79A and CD45RO and negativity for Bcl-6, CD30, CD15 (Figure 5) and CD10 (not presented).

This immunohistochemical profile oriented the diagnosis towards T-cell/histiocyte-rich large B-cell lymphoma.

The panel was completed with other two antibodies, in order to assess the tumor aggressiveness and prognosis, i.e., Ki67 and Bcl-2. Both were positive (Figure 6). Moreover, the Ki67 index was 34%.
The neoplastic proliferation was grossly identified only in the kidney and the CD20 and DC79A immunostaining confirmed the presence of neoplastic B-cells in the interstitial lymphocytic infiltrate of renal parenchyma (Figure 7).

Figure 5 – Immunohistochemical panel for tumoral cells. Top: Positive immunostainings for atypical B-cells, ×400 (large images), ×100 (roundels). Bottom: Negative immunostainings for atypical B-cells, ×100.

Figure 6 – Positivity of prognostic (Bcl-2) and aggressiveness (Ki67) factors, ×400 (large images), ×100 (roundels).

Figure 7 – Kidney infiltration. Left: Diffuse lymphocytic infiltrate in renal interstitium, HE staining, ×100. Center and right: Neoplastic cells positive for CD20 and CD79A, ×200.
Discussion

The first issue face to such a spectacular tumor mass that has resulted in such a tragedy was to establish a correct diagnosis. From the many possibilities of marking the tumor for an accurate identification, we could use a wide panel of 15 antibodies that covered all cellular members of the neoplastic proliferation.

The great variety of used antibodies allowed us not only to assign the correct label to the cellular proliferation but also to differentiate it from other lymphoid malignancies (Table 1).

The immunohistochemical investigation panel was completed with the AE1/AE3 antibody that revealed the remnants of the thymic epithelial network.

Table 1 – Immunohistochemical distinction between TC/HRLBCL and DLBCL/PMLBCL, CHL and PTCL

<table>
<thead>
<tr>
<th>Staining</th>
<th>Favor TC/HRLBCL</th>
<th>Favor DLBCL/PMLBCL</th>
<th>Favor CHL</th>
<th>Favor PTCL [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usually (+) in TC/HRLBCL</td>
<td>(+)</td>
<td>(+ strong, uniform)</td>
<td>(+) / (+ weak, variable)</td>
<td>(-)</td>
</tr>
<tr>
<td>CD20</td>
<td>(+)</td>
<td>[17, 20–24]</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>CD79A</td>
<td>(+)</td>
<td>[20–24]</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>CD45RO</td>
<td>(+)</td>
<td>[17, 22]</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>Bcl-6</td>
<td>(−)</td>
<td>[22, 25]</td>
<td>(+)</td>
<td>variable</td>
</tr>
<tr>
<td>MUM-1</td>
<td>(+)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD19</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD22</td>
<td></td>
<td>[25]</td>
<td>(+)</td>
<td></td>
</tr>
<tr>
<td>PAX5</td>
<td>(−)</td>
<td>[20, 21, 23]</td>
<td>(+)</td>
<td>(+ strong)</td>
</tr>
<tr>
<td>OCT2/BOB1</td>
<td>(−)</td>
<td>[23]</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>EMA</td>
<td></td>
<td>[22, 25]</td>
<td>(+ variable)</td>
<td></td>
</tr>
</tbody>
</table>

| Usually (−) in TC/HRLBCL | (+) | (− weak, variable) | (+) / (−) |
| CD30 | (−) | (+ weak) | (+ weak) / (+) |
| CD5 | (−) | [17, 22–25] | (+) |
| CD10 | (−) | [22, 25–26] | (+) / (+) |
| CD15 | (−) | [17, 22–25–27] | (+) / (−) |
| EBER | (−) | [25] | exceedingly rare |
| CD43 | (−) | [25] | |
| CD138 | (−) | [25] | |
| p63 | (−) | [25] | |

Prognostic factors

| Bcl-2 | (−) | [15–30%] | (−) |
| Ki67 index | 34% | 15–30% | 30–40% | (+) |

The non-neoplastic stromal environment

| CD2 | (+) | [24] | (+) |
| CD3 | (+) | [22–25] | (+) |
| CD5 | (+) | [22–25] | (+) |
| CD7 | (+) | [23, 24] | (+) |
| CD8 | (+) | [23–25] | CD8+ |
| CD4 | (+) | [23, 24] | CD4+ |
| CD45RO | (+) | [22–25] | (+) |
| IgD | (+) | [25] | (+) |
| CD56 (NK) | (+) | [23, 24] | (+) |
| BetaF1 | (+) | [23, 24] | (+) |

Histocytes

| CD68 | (+) | [22, 25] | (+) |
| CD16 | (+) | [25] | (+) |

Dendritic cells

| CD21 | (+) | [22, 25] | (+) |
| CD23 | (+) | [17, 22, 25, 26] | (+) |

a: Thymus; b: Kidney; c: Lymph nodes; Blue color: Our antibody panel; CHL: Classical Hodgkin’s lymphoma; DLBCL: Diffuse large B-cell lymphoma; EBER: Epstein–Barr virus-encoded small RNAs; PMLBCL: Primary mediastinal large B-cell lymphoma; PTCL: Peripheral T-cell lymphoma; TC/HRLBCL: T-cell/histiocyte-rich large B-cell lymphoma; EMA: Epithelial membrane antigen; NK: Natural killer.
First of all, the tumor fulfilled the four main criteria stated by Achten et al. in 2002 [29], in order to be considered T-cell/histiocyte-rich B-cell lymphoma, the newly recognized variant of diffuse large B-cell lymphomas, criteria that we remind further:

- Effacement of the thymic architecture due to the neoplastic infiltrate with diffuse or vaguely nodular pattern;
- Presence of large neoplastic B-cells that do not express CD15, that account for a minority of the total cell population and occur singly or in small clusters;
- Prominent background infiltrate, composed of both T-cells and non-epithelioid histiocytes;
- Minimal presence of small reactive B-cells in neoplastic areas [29].

The positive diagnosis was supported by:

- Presence of atypical neoplastic B-cells positive for CD20, CD79A and CD45RO and negative for CD5, CD10 and CD15;
- Background lymphocytic proliferation with CD3/CD5 profile, CD45RO positive and with a T-cells ratio in favor of CD8+ cells;
- Presence of CD68+ histiocytes;
- Absence of CD30+ dendritic cells.

What differed somehow from the immunohistochemical profile described in the literature for this particular B-cell malignancy was the negativity for Bcl-6, usually reported as positivity and the negativity of CD30, which is reported as weak positive in subsets only however (Table 1).

Finally, the tumor was aggressive, with a Ki67 index of 34%, which explained its rapid growth to such impressive dimensions and had a signaled potential poor prognosis by the positivity of Bcl-2.

Further, it was important to distinguish the proliferation mainly from classical Hodgkin’s lymphoma (CHL) and peripheral T-cell lymphoma (PTCL), with which it may be easily confused [11, 30–32].

For the exclusion of CHL pleaded the negativity of CD30, CD15 and CD23 and the T-cells ratio in favor of CD8+ T-cells and for the exclusion of PTCL pleaded the positivity of B cells markers (CD20 and CD79A) the negativity of CD30 and also the T-cells ratio in favor of CD8+ T-cells. The differentiation from DLBCL/PMLBCL consisted of negativity of CD30 and CD23, markers reported as positive in DLBCL/PMLBCL (Table 1).

The second issue was the comparison of our case with the other case with thymic involvement published in the literature, summarized in Table 2 and with data concerning TC/HRLBCLs in their usual location, i.e., lymph nodes.

Table 2 – Comparison between our case and Xu et al. case [3]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Xu et al.</th>
<th>Our patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>Age</td>
<td>52 years</td>
<td>Four years and six months</td>
</tr>
<tr>
<td>History</td>
<td>Sjögren’s syndrome</td>
<td>Fatigue at moderate effort in the last weeks</td>
</tr>
<tr>
<td>Onset</td>
<td>Sudden – chest pain</td>
<td>Sudden – air hunger, Superior vena cava syndrome, Cardiorespiratory arrest resuscitated, Coma</td>
</tr>
<tr>
<td>CT</td>
<td>Large anterior mediastinal mass. Several enlarged mediastinal lymph nodes.</td>
<td>Brain: bilateral effacement of fissures; lateral ventricles with reduced dimensions; diffuse cerebral edema. Huge mediastinal mass (13.5 cm in largest diameter) who compresses the heart and the lungs (collapse of the right lung and atelectasis of left inferior lobe) and embeds and compresses main mediastinal vessels, trachea and main bronchi. Right pleural effusion. Hepatomegaly, splenomegaly.</td>
</tr>
<tr>
<td>HP</td>
<td>Thymoma, lymphocyte predominant type. Benign reactive lymph nodes.</td>
<td>Thymic TC/HRLBCL</td>
</tr>
<tr>
<td>Outcome</td>
<td>Postoperative: uneventful. One year later: • Clinical: – night sweats, low grade fever, flu-like symptoms, green sputum production, 14 lb/6.4 kg weight loss, and some shortness of breath with exertion. • CT: – multiple enlarged lymph nodes throughout the chest and upper abdomen; – multiple new non-calcified pulmonary nodules; – bilateral pulmonary dense consolidation.</td>
<td>Deceased</td>
</tr>
</tbody>
</table>

F: Female; M: Male; CT: Computed tomography; HP: Histopathology; TC/HRLBCL: T-cell/histiocyte-rich large B-cell lymphoma.
The first difference between our case and the case presented by Xu et al. [3] is patient’s gender and age. While our case was a very young boy of almost five years of age, the other case was that of a woman in the sixth decade of life (Table 2). Literature data referring to lymph nodes and extranodal sites other than thymus are speaking about a mean age varying between 30 and over 60 years and a male predominance [11, 12, 24, 25, 29, 33–37].

Another difference is about the onset. While the American woman complained of a sudden chest pain, but which allowed her to be investigated, operated and monitored for one year, our young boy had a dramatic onset with sudden air hunger, followed rapidly by cardiorespiratory arrest, which required several resuscitation procedures which, until the end could not help him.

Another difference is the disease spread. While the American patient had several mediastinal lymph nodes involved at the onset and then, “a year later, multiple enlarged lymph nodes throughout the chest and upper abdomen, multiple new non calcified pulmonary nodules, and bilateral pulmonary dense consolidation” [3], our case had no lymph nodes, hepatic and splenic involvement (even if the liver and spleen were enlarged for the age) but obvious from the gross examination renal involvement, proved also immunohistochemically.

Another difference has concerned the case evolution. Our young patient died shortly after the onset and despite all resuscitation procedures and intensive treatment applied. This meant that, on one hand, no therapeutic protocol addressed to the malignant proliferation could be set up and, on the other hand, that the tumor was very aggressive. One proof is its rapid growth, with severe compression on mediastinal structures and especially on the heart and the main aortic branches, which resulted in superior vena cava syndrome, followed by coma and death. The other proof was brought by the immunohistochemical assessment, which showed a high Ki67 index and the positivity of Bcl-2. Finally, another proof was the spread outside the thymus, which was, however, atypical with the involvement of the renal parenchyma only.

Conclusions

Besides its statistical value, by reporting the second case in the literature with primary involvement of the thymus by this rare variant of diffuse large B-cell lymphoma, this case represents also a lesson. That means any clinical symptom of unexplained fatigue and dyspnea in a child should raise the clinician’s suspicion of a mediastinal mass involving the thymus, which has to be investigated rapidly and using compulsorily the histopathological examination as the golden standard for the diagnosis. In this way, not only rare diseases are discovered but lives can be saved.

Conflict of interests

The authors declare that they have no conflict of interests.

References


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