We report the atypical case of posttransplant lymphoproliferative disorder (PTLD) diagnosed in a 55-year-old man 9 years after renal transplantation. It was evaluated only by bone marrow biopsy, which showed its total involvement with malignant lymphoma. It was composed of two populations of lymphoid cells: large RS-like cells and small to medium ones, with slightly angular nuclei without visible nucleoli. Both cell populations did not show positive reaction for typical B cell markers (CD20, CD79a). Large RS-like cells were positive with CD30 and EBV-LMP. However, negative reaction with CD15 and positive reactions with UCHL1 and EMA were not consistent with classical type of Hodgkin lymphoma. Morphological picture and immunophenotype had suggested anaplastic T cell lymphoma. Because of negative reaction with ALK1, initial diagnosis was ALCL ALK-negative. Then, additional stains with BOB1 and Oct2 were performed, which were positive. Taking it into account the diagnosis was changed; finally Hodgkin-like B lymphoma was diagnosed. The patient was treated with CHOP regimen with good response. 5 years after primary diagnose of PTLD he is still free of disease. Conclusions: 1. Apart from typical forms of PTLD, one may expect cases with nonspecific morphological picture and phenotype. 2. Negative reactions with typical immunohistochemical markers for lymphocytes of B cell line do not exclude the possibility of B-cell proliferation.

Introduction

Posttransplant lymphoproliferative disorders (PTLD) are well-known complication in both solid organs and bone marrow transplants recipients. The incidence of PTLD ranges from 1 to 10% of these patients and depends mainly on the type of transplanted organ and the intensity of the immunosuppressive therapy used [3, 24, 31, 39]. In the case of kidney transplantation it is reported in about 0.66-2% of patients [7, 37, 39, 41, 47]. The occurrence of PTLD is the consequence of severely depressed immunity by prolonged immunosuppressive treatment, or in cases of bone marrow transplantation, by therapeutic decrease of T cells in donor’s bone marrow, what diminishes risk of GVHD [48]. Essential role in the development of the disease plays Epstein-Barr virus infection [1, 35, 37, 47]. Especially bad course of the disease is observed in patients seronegative for EBV virus before the transplantation with the seroconversion after the transplantation, because of primary EBV infection [1, 2, 23].

We present here considerable diagnostic difficulties in atypical case of Hodgkin-like lymphoma, accompanied with EBV infection, which occurred in 55 year old patient 9 years after renal transplantation.
Clinical history

55-years old male kidney recipient was admitted to the hospital because of general weakness. 9 years ago he was transplanted because of polycystic renal disease. During one month after transplantation he obtained the immunosuppressive treatment in standard doses (cyklosporine, encorton, azathioprine), later reduced because of signs of liver damage. During follow up EBV and HCV infection were serologically confirmed; episodes of transplant rejection were not observed. Patient had twice basal cell carcinoma surgically removed from his cheek.

By admission physical examination showed no significant pathology. Ultrasound examination revealed lymph nodes in the hilus of the liver and in paraaortic region below coeliac trunk enlarged to 2cm and single cyst about 1.5cm in diameter in the liver. Biochemical tests confirmed normal function of the transplanted kidney. Beside slight pancytopenia there were no other pathologic changes in blood cell count; blood smear was normal. Serological tests showed active EBV infection with possibility of reactivation (VCA IgM-; VCA IgG+; EA(D) IgG+; EBNA IgG+), and HCV infection; there was no HBV infection. Patient underwent diagnostic bone marrow and inguinal lymph node biopsies. Bone marrow was totally involved with malignant lymphoma; lymph node showed only lipomatous atrophy with no lymphoma infiltration. Because of the diagnosis of PTLD immunosuppressive treatment was reduced (cyclosporine 2x 50mg). The patient obtained antiviral (gancyclovir 3 times a week, later heviran) and chemotherapeutic treatment according to CHOP scheme (7 courses during four months). The improvement in patient’s general condition was observed. Bone marrow biopsy performed four months after initial diagnosis revealed significant bone marrow hypoplasia without neoplastic infiltration. Six years after primary diagnose of PTLD patient is feeling well; there is no disease recurrence. Function of the transplanted kidney is preserved.

Material and Methods

Bone marrow biopsy 2.3cm long was fixed in Oxford fixative. 4 μm thick sections were stained with hematoxyline and eosin and with Gomori method. The following immunohistochemical stains were performed: LCA, CD20, CD79a, CD3, CD30, CD15, OPD4, UCHL1, CD5, CD56, CD34, CD31, EMA, BH9, Vs38c, Bcl2, EBV (LMP), Alk1, Ki67, Granzym B, Oct2, BOB1, BSAP/PAX-5gene product. Molecular test: IgVH, TCR beta and gamma were performed as well.

Results

Histological examination of the material revealed total involvement of the bone marrow with malignant lymphoma composed of two populations of lymphoid cells: small and medium ones, with slightly angular nuclei without visible nucleoli and with narrow rim of cytoplasm, and polymorphic, large RS-like cells (Fig.1). Large cells had multilobular follicular nuclei, most of them contained distinct single or double nucleoli. All RS-like cells had abundant, basophilic cytoplasm. Numerous plasma cells were located mostly around vessels. Only single islets of hemopoietic tissue were noticed. Gomori stain showed slight increase in reticulin network of the stroma. Results of immunohistochemical stains are presented in Table 1.

Taking under consideration clinical data, morphology and phenotype of the cells ALK- negative anaplastic T cell lymphoma was primarily diagnosed. The case was presented on XI Meeting of European Association For Haematopathology in Siena in 2002. International panel of pathologists had suggested rather PTLD Hodgkin-like lymphoma, than anaplastic lymphoma. Additional immunohistochemical and molecular investigations were performed. Positive reactions with BOB1 and Oct2 antibodies were obtained (Fig.2), but stain with the use of BSAP was unreliable. Also the molecular studies, probably because of DNA changes due to the routine fixing methods and decalcification of the material were unreliable.

Discussion

PTLD include heterogenous group of lymphoid proliferations occurring in transplant patients with remarkably variable clinical presentation varying from hyperplastic

Fig.1. H&E Hodgkin-like lymphoma – RS-like cells.
TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>RS-like cells</th>
<th>Small/medium cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCA</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>UCHL1</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>EMA</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>CD20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CD79a</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CD15</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CD56</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CD31</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BHH9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ALK1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CD34</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CD3</td>
<td>+ single cells</td>
<td>+</td>
</tr>
<tr>
<td>OPD4</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>CD5</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>Bcl2</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>CD30</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>EBV(LMP)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>GranzB</td>
<td>+ single cells</td>
<td>-</td>
</tr>
<tr>
<td>Ki67</td>
<td>60%</td>
<td>40%</td>
</tr>
<tr>
<td>BOB1</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Oct2</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>BSAP/PAX-5 gene product</td>
<td>unreliable</td>
<td>unreliable</td>
</tr>
</tbody>
</table>

reactive reactions to neoplastic growth with highly aggressive course. Most of PTLD – over 85% - derive from B cells [1, 5, 18, 21, 52].

Among them, according to the WHO classification [21] there is distinguished separate group, which includes Hodgkin lymphoma and Hodgkin-like lymphoma. Both forms: classic Hodgkin and Hodgkin-like lymphoma are rare diseases in solid organs recipients [6, 12, 14, 30, 32, 38, 42, 46, 47]. They are a little more common after allogenic bone marrow transplantation [4, 40]. Classic Hodgkin lymphoma is usually diagnosed on the base of its typical morphologic picture with confirmation of the phenotype (CD15 and CD30 positive). Some authors consider that Hodgkin lymphoma is extremely rare in posttransplant patients and...
reports describing such cases were referred to the Hodgkin-like lymphoma indeed. The latter might be identical to the classical form, but large RS-like cells, being active immunoblasts, are positive for LCA, CD30 and B lymphocytic markers [16]. Positive reaction with CD15, characteristic for Hodgkin lymphoma in this case is negative. In our case cells resembling classic RS-cells were multiple, and in the beginning diagnose of Hodgkin disease was relatively most probable. Immunohistochemical analysis for CD30 has been positive (Fig.3), but for CD15 negative. These cells showed also positive reactions with LCA and EMA. There were T-rosettes around RS-like cells, however, the fibrosis and reactive stroma, characteristic for Hodgkin lymphoma was not present. According to widely accepted criteria, the diagnosis of classic Hodgkin lymphoma was rather unreliable. Because immunohistochemical reactions for lymphomas deriving from B lymphocytes (CD20, CD79a) were negative as well, in the beginning, we excluded B cell Hodgkin-like lymphoma. At the same time positive reaction for CD30, UCHL1, EMA and LCA in all RS-like cells and CD3 and granzyme B in few of them have suggested T cell anaplastic lymphoma.

Among still growing amount of reports describing uncommon for PTLD malignant lymphomas, both B (like MALT type lymphoma [19, 45], Burkitt’s lymphoma [3, 26, 44, 47, 49], mantle cell lymphoma [27, 52] or multiple myeloma [6, 33, 50]) and T cell derivations [15, 34] there are also some anaplastic lymphomas [9, 22, 43].

Epstein-Barr virus infection is supposed to be a main causative factor of PTLD, especially derived from B cells. Early in the course of the infection the EB virus infects B lymphocytes via binding to the cell surface CD21 receptor. This decreases the rate of apoptotic cell death through the induction of bcl-2 and stimulates their extensive proliferation. T lymphocytes dysfunction, secondary to immunosuppressive treatment may lead to the development of B cell lymphoma [10]. In our case positive immunohistochemical reaction with antibody anti-EBV (LMP1) was obtained and reactivation of this infection in serological tests was confirmed as well. It seems that connection between PTLD and EBV in our case is obvious and this fact suggests rather B cell than T cell etiology of the disease. We should emphasize, that in cases of PTLD of T and NK line EBV infection is less common, but may be present as well in quite big amount of patients [37, 51]. Simultaneous infection of B and T lymphocytes with accompanying clonal proliferation of both cellular lines is also possible [8].

Among other risk factors of PTLD development there are HCV [7, 17, 29] and cytomegalovirus infections [23]. Hezode et al. described 4 cases of PTLD in patients after liver transplantation with coexisting HCV infection [17]. Three of these patients developed the disease in extrahepatic sites. They have found that PTLD occurrence is higher in patients, who undergone transplantation because of liver cirrhosis due to HCV infection (10.5%), in comparison with patients transplanted because of other causes (1.7%). All described cases were B lymphocytes proliferations. Hsi et al. described 3 cases of posttransplant MALT lymphoma; one of them was a 63-year old woman after liver transplant because of HCV infection [19]. In our case chronic HCV infection was present as well. In available references we have not found reports of coexistence of T – PTLD with HCV infection. This fact does not exclude the diagnosis of T cell lymphoma, of course, but is in favor of B cell proliferation.

The next problem to consider was negative result for ALK1. Most anaplastic lymphomas are positive for ALK1, what detects translocation t(2;5) between gene ALK located on chromosome 2 and nucleophosmin gene on chromosome 5 [21]. ALCL in older individuals are more often negative with ALK1. In both types of ALCL lymphoma nodal and extranodal involvement at the same time is quite common, bone marrow involvement reaches 30% [13], but ALK1 negative lymphomas rarely show extranodal setting [21]. In our case probably there were both: nodal (paraortic and in the hilus of the liver) and bone marrow involvement. Peripheral lymph nodes were not enlarged. Because the satisfactory diagnosis was made based on the trephine biopsy, aggressive laparoscopic abdominal lymph node biopsy was not performed. Available for investigation small inguinal lymph node was unchanged.

Most posttransplant T cell lymphomas show very aggressive course and lead to patient death in a very short time [15, 25]. In our case the patient achieved complete remission and is free of disease after six years.

Additionally performed positive immunohistochemical stains for Oct2 and BOB1 made us to change the previous diagnosis of ALK negative, T-cell anaplastic lymphoma. BOB1 and Oct2 are transcription factors labeling normal and neoplastic B cells [21]. However, some last reports show their possible expression in human T cell neoplasms [28]. On the other hand expression for both Oct2 and BOB1 points on Hodgkin-like lymphoma, although does not exclude Hodgkin lymphoma, as well [21]. Immunostains with BSAP/PAX-5, which, if positive, would have definitely ruled out the possibility of an ALK negative ALCL failed, as the antigen was not well preserved. Genetic tests were also performed, but because of a long time interval between the obtaining of the material to test performance, its results were not reliable and they did not bring ultimate solution.

Taking into consideration, all available data: morphological, phenotype and clinical features, the diagnosis of Hodgkin-like B cell lymphoma was established. A very good response for treatment is as well a factor which might
confirm the diagnosis. There are also another malignant neoplasms in posttransplant patients treated with immunosuppression, besides immunoproliferative disorders. The most common are skin cancers, Kaposi sarcoma, carcinomas of the vulva and cervix, gastroenteric tumors, kidney and urinary tract cancer. Our patient was previously twice surgically treated because of basal cell carcinoma on the face. In spite of so many diagnostic problems in this particular case, the treatment applied was fully effective — the patient is still well, showing no symptoms of lymphoma recurrence.

In conclusion: 1. Apart from typical forms of PTLD, one may expect cases with nonspecific morphological picture and phenotype.

2. Negative reactions with typical immunohistochemical markers for lymphocytes of B cell line (CD20, CD79a) do not exclude the possibility of B-cell proliferation.

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