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Post-Transplant Lymphoproliferative Disorder after Autologous Hematopoietic Cell Transplantation for Hodgkin's Lymphoma

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Abstract. Post-transplant lymphoproliferative disorder is a very rare complication post autologous bone marrow transplant with few cases reported so far. We report a case of a child with history of classic Hodgkin's lymphoma, nodular sclerosis type, who was treated with autologous stem cell transplantation. Three months after the transplant, he developed bilateral cervical lymphadenopathy, splenomegaly, neutropenia and thrombocytopenia. Excisional biopsy of a left cervical lymph node revealed a post-transplant lymphoproliferative disorder. The morphological pattern of this post-transplant lymphoproliferative disorder was combined monomorphic and polymorphic, with plasmacytoid/plasmablastic differentiation expressing CD20 and CD79A. Kappa and lambda light chain immunohistochemistry stains showed a clear evidence of lambda light chain restriction. Immunohistochemistry stain and in situ hybridization for Latent membrane protein-1 were positive for Epstein-Barr virus. Polymerase chain reaction study revealed monoclonal B-cell proliferation with immunoglobulin heavy chain gene rearrangement. The patient was treated with prednisolone as 2 mg/kg/day over 2 weeks with tapering over the following 3 months. The white cell count recovered with regression of splenomegaly and cervical lymphadenopathy. On his last visit to the outpatient clinic, two years after the diagnosis of post-transplant lymphoproliferative disorder, he was in good health with normal laboratory parameters.

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Introduction

Post-transplant lymphoproliferative disorder (PTLD) is a complication of allogeneic bone marrow transplantation (BMT). Rare cases of PTLD after autologous BMT have been reported mainly in adults. This is not surprising, considering the fact that the incidence of PTLD after allogeneic BMT is only 1%, and that autologous stem cell transplantation (ASCT) is associated with less immunosuppression than allogeneic BMT[1]. Lones *et al.* reported the first case of PTLD after autologous BMT[2] in a paediatric patient. Risk factors have not been defined for ASCT, but some authors have speculated on the role of T-cell depleting the autograft, concurrent CMV infection, and impaired cytolytic T-cell response, specifically to Epstein-Barr virus (EBV)[2,3]. PTLD after autologous BMT in paediatrics is extremely rare. In this report, we describe a case of PTLD in a paediatric patient after autologous BMT**.**

Case History

A 13-years-old Saudi male was diagnosed in August 2004 as a case of nodular sclerosis Hodgkin's Lymphoma (Fig. 1A-B). The patient stage was 4BS. The primary disease was in the left inguinal (bulky), right inguinal and in the right and left cervical lymph node groups. CT scan revealed multiple lung nodules and splenomegaly. Bone marrow was not involved. He was treated as per the United Kingdom Childrens' Cancer Study Group for Hodgkin's Disease (UKCCSG HD 2002 02 protocol) with four cycles of ABVD (adriamycin, bleomycin, vinblastine, and decarbazine) and four cycles with COPP (cyclophosphamide, vincristine, procarbazine, and prednisone). He finished the treatment in March 2005. No radiotherapy was given. The patient stayed in complete remission for two and half years. On September 2007, he suffered with fever and weight loss for one month. Physical examination revealed left inguinal mass and splenomegly. CT scan revealed left superficial and deep inguinal, bilateral cervical, para-aortic and mediastinal lymphadenopathy with splenomegaly. Histopathological review of the left inguinal mass confirmed the relapse of Hodgkin's' Disease. Bone marrow was not involved. He was treated with four cycles of EPIC (etoposide, prednisone,

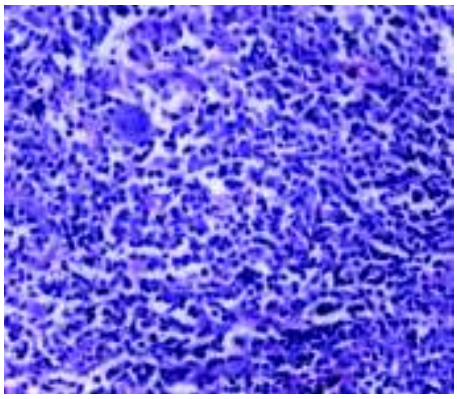

Fig. 1A. Reed-Sternberg cell identified in the original lymph node biopsy that shows classic Hodgkin's lymphoma (Hematoxylin and Eosin stain, original magnification X400).

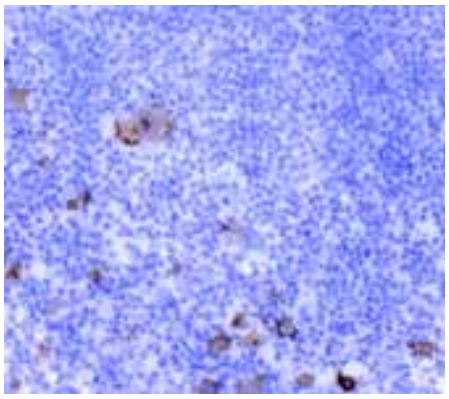

Fig. 1B. Reed-Sternberg cell showing positive staining for CD30 (original magnification X400).

ifosphamide, cisplatinum) followed with stem cell mobilization with GCSF (granulocyte colony stimulating factor) and autologus bone marrow transplantation. He received BCNU, cytrabine, etoposid and melphlan as conditioning myeloablative chemotherapy. The total CD34 dose given was 2.55 x10^6 /kg. Radiation to the left iliac lymph nodes was given post transplantation (total dose of 2160 over 11 fractions). Follow up scans showed that the patient was in a complete remission. Three months after the transplant, however, he developed bilateral cervical lymphadenopathy, splenomegaly, neutropenia and thrombocytopenia. CT scan showed enlarged cervical LN with splenomegaly. An excisional biopsy of a left cervical lymph node was done in June 2008. Morphological assessment of the excised cervical lymph node revealed features of PTLD with a complete effacement of the normal lymph node architecture by a diffuse proliferation of hematolymphoid cells. The lymphoid population included small cleaved lymphocytes, plasma cells, plasmablasts and immunoblasts, some of which appeared atypical. The mitotic rate was high, and apoptotic bodies were easily identified. Monomorphic and polymorphic areas were seen. Immunohistochemical staining revealed the majority of the large immunoblastic cells to be of B-cell phenotype (CD20 and CD79A positive) (Fig. 2A-D). Striking predominance of cytoplasmic lambda light chain was apparent by immunohistochemistry stains. Using standard polymerase chain reaction (PCR) methodology, a strong immunoglobulin heavy chain (IgH)

rearrangement was also found. Immunohistochemistry stain and in situ hybridization for EBV (LMP-1) were positive (Fig. 2E). The overall findings were those of EBV associated with PTLD of the monomorphic type with polymorphic areas, and a clear evidence of B-cell monoclonality. Bone marrow was negative. He received treatment with prednisolone as 2 mg/kg/day over 2 weeks with tapering over the following 3 month. The WBC and platelet count were recovered with regression of spleen and cervical LN to normal size. On his last visit to the outpatient clinic, his physical examination and laboratory parameters were all normal.

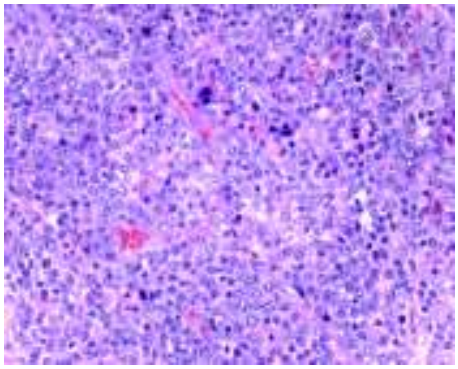

Fig. 2A. **High magnification of a field showing a monotonous population of abnormal cells with plasmablastic features (Hematoxylin and Eosin stain, original magnification X400).**

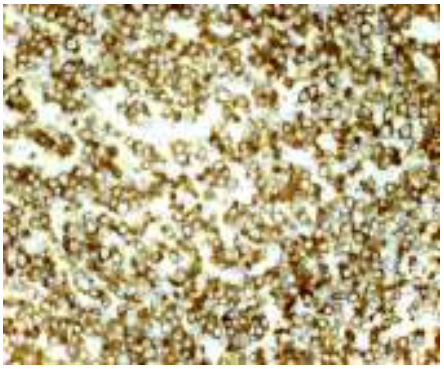

Fig. 2B. **Immunohistochemistry staining for CD79A shows the majority of the cells are positive (original magnification X400).**

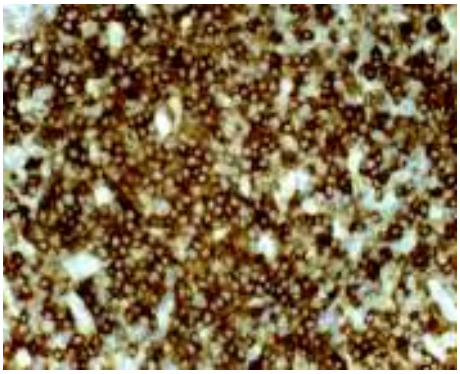

Fig. 2C. **The majority of tumor cells express lambda light chain by immunohistochemistry (original magnification X400).**

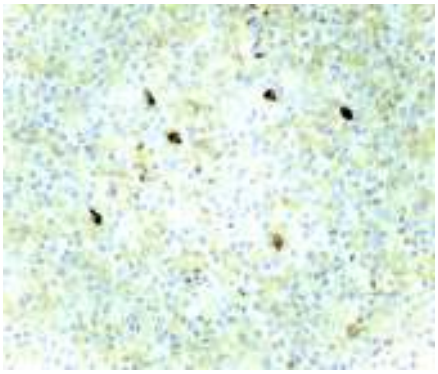

Fig. 2D. **Kappa light chain is expressed only in rare isolated cells (original magnification X400).**

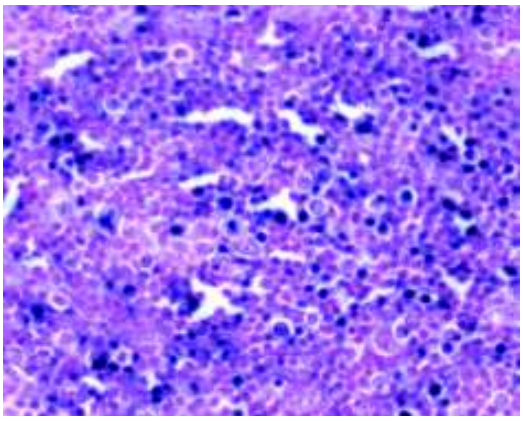

Fig. 2E. ***In-situ*** **hybridization for EBV showing many positive cells (original magnification X400).**

Discussion

PTLD represents a spectrum of lymphoproliferative diseases seen as a result of immunosuppression in recipients of solid organ or hematopoietic stem-cell transplantation. PTLD is a known complication of both, solid organ transplantation and allogeneic BMT, but is rarely seen following autologous BMT[2,4-9]. Despite over 20 years of experience with autologous bone marrow transplantation, very few cases of PTLD have been reported[2,10-13]. PTLD is thought to be related to a high degree of immunosuppression allowing unregulated proliferation of EBV transformed B-lymphocytes[14]. While most cases are EBV related, there is a small subset of patients with T-cell lymphomas that are EBV negative[15].

A case of PTLD in the context of autologous stem cell transplantation (ASCT) for Hodgkin's lymphoma is reported. In this case, the presence of EBV was confirmed by immunohistochemistry and *in situ* hybridization. Clonality was also confirmed by immunohistochemical stains that demonstrated immunoglobulin light chain restriction (lambda), as well as by PCR that demonstrated IgH gene rearrangement. The presentation of PTLD post ASCT in our case was early. In PTLD, EBV causes a spectrum of changes ranging from hyperplasia to frank malignancy. Three categories are now recognized: plasmacytic hyperplasia, polymorphous PTLD and monomorphic PTLD/malignant lymphoma/myeloma[14]. This classification has proved useful as it helps predict a response to therapy. In the hyperplasia group,

tumors will often regress with reduction of immunosuppression, whereas monomorphic PTLDs tend to be refractory to therapy. Our patient falls in between the second and third morphological categories with monomorphic and polymorphous patterns. There is no standard treatment for PTLD following ASCT; however, treatment options included antivirals, lymphocytotoxic therapy or immune modulation[7,16]. In EBV infected cells, gancyclovir has been shown to be superior to acyclovir[17]. Gancyclovir is likely to be effective only with early lytic EBV infection and probably will not alter the replication of latently infected B-cells[1]. Unfortunately, data on gancyclovir in PTLD are limited, but remission was achieved in some cases[7,18]. However, there are three previously reported patients treated with gancyclovir in the post-ASCT setting, all of whom died of their disease[2,8,13]. Other treatments that have been undertaken include IVIG, IFN, acyclovir and steroids[7,10,11,13,19-23]. Recently anti-B-cell monoclonal antibodies have shown promising results in patients with PTLDs. In a subgroup of BMT patients, nine of 10 patients with oligoclonal PTLD achieved a complete remission (CR) with anti-CD21/24 antibodies[24]. A recent retrospective analysis of solid organ transplant and BMT patients using rituximab showed a 54% CR rate, and a 69% partial remission (PR) rate in 32 patients[25]. Similar result has been reported by Kuehnle *et al.*[26]. Takahashi *et al.* reported a patient with EBV-associated monomorphic PTLD after autologous peripheral blood stem cell transplantation who died 155 days after transplantation despite treatment with rituximab and hydroxyurea[6]. T-cell PTLD has been also reported after autologous blood stem cell transplantation[8]. In summary, this study reports a rare EBV associated PTLD in a paediatric patient after autologous BMT who responded to steroid therapy.

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اضطراب التكاثرية اللمفاوية ما بعد زرع الخلايا المكونة للدم لسرطان هودجكين للعقد اللمفاوية

جوده أحمد المغربي[1،2]، و حسان هاشم صيادي[2]، و نبيله محمد الباز[2]، ومحمد صلاح الدين بيومي[3]

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المستخلص. اضطراب التكاثرية اللمفاوية ما بعد زرع نخاع العظم الذاتي هو أحد المضاعفات النادرة جدًا. نحن نقدم تقريرًا لحالة طفل مصاب بليمفوما هودجكين الكلاسيكية، تم علاجه بزراعة خلايا جذعية ذاتية. بعد مضي ثلاثة أشهر، ظهر ورم في العقد اللمفاوية في الرقبة، وتضخم في الطحال. الفحص النسيجي أظهر وجود اضطراب تكاثرية لمفاوية ما بعد الزراعة لخلايا من النوعين المتشابه والمختلف، وأظهرت اعتصارًا للخلايا من نوع ب. التحليل الجزيئي وتحليل الصبغات المناعية أظهر وجود وحدة جينية. كذلك الصبغات المناعية والوميضية لفيروس الايبيشتاين بار كانت إيجابية. عولج المريض بالستيرويدات لمدة أسبوعين تم إنقاصها التدريجي على مدى ثلاثة أشهر، واستجاب المريض بشكل جيد. في آخر زيارة للمريض كان بصحة جيدة بعد مرور سنتين من التشخيص.