CASE REPORT – OPEN ACCESS

International Journal of Surgery Case Reports 38 (2017) 115–118

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.casereports.com

Post-transplant lymphoproliferative disorder and management of residual mass post chemotherapy: Case report

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ARTICLE INFO

Article history:
Received 12 May 2017
Received in revised form 29 June 2017
Accepted 3 July 2017
Available online 8 July 2017

Keywords:
Case report
Post-transplant lymphoproliferative disorder
Debulking surgery
Retroperitoneal tumor
Residual mass
Ritixumab

ABSTRACT

INTRODUCTION: Post-transplant lymphoproliferative disorder (PTLD) is a rare complication. It represents a spectrum of lymphoid proliferations which occur in the setting of immunosuppression and organ transplantation. There are no reported cases or recommendations for the treatment of residual masses post rituximab of PTLD.

PRESENTATION OF CASE: A patient with a long standing history of immunosuppression due to multiple kidney transplants starting in 1979, presented with a very large palpable hard abdominal mass (2004) after a fourth renal transplant. There was a past history of heavy immune suppression. CT scans revealed a conglomerate mass involving the right native kidney and two prior right sided renal allografts that crossed the midline. Biopsy of the large right retroperitoneal mass revealed large B cell lymphoma (CD 20 positive); consistent with post-transplant lymphoproliferative disorder (PTLD).

DISCUSSION: Management of bulky PTLD, in a highly sensitized, heavily immune suppressed patient is not well described in the literature. The mainstay of therapy is IR and Ritixumab (R) monotherapy and combination R-CHOP. CHOP chemotherapy has an associated mortality rate of up to 38%. Radiotherapy is often considered over surgery and surgery has been most frequently used when associated with bowel complications. In this case report we describe upfront Ritiximab followed by consolidation resection and cytotoxic chemotherapy as a management strategy to reduce toxicity.

CONCLUSION: The approach taken by our surgical team illustrates the benefits of disease debulking in certain cases of PTLD, by guiding further therapy and spacing and reducing chemotherapy in immune suppressed patients.

1. Introduction

The present work has been structured in line with the SCARE guidelines [1]. Post-transplant lymphoproliferative disorder (PTLD) is a well known albeit rare complication, occurring in approximately 1% of renal transplants [2]. It represents a spectrum of lymphoid proliferations which occur in the setting of immunosuppression and organ transplantation. It is also generally an Epstein-Barr Virus (EBV) associated proliferation ranging from lymphoid hyperplasia to high grade lymphoma and is mostly of B-cell origin. Active EBV infection is associated with the development of PTLD and seronegative transplant recipients who acquire primary EBV infection in the post-transplant period are at an elevated risk of developing PTLD. Mortality of PTLD can be high, but varies between centers and also depends on the type of organ transplanted [3].

Initial treatment of PTLD is immunosuppression reduction (IR). If the disease is localized treatment options include surgery or radiotherapy [4]. However, in the majority of cases PTLD is detected as multifocal disease. Standard treatment includes rituximab, a monocloncal antibody targeted to CD20, alone or in combination with chemotherapy consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Generally, patients will be treated with IR and rituximab monotherapy, and if they fail to respond or have clinically aggressive disease, will be given rituximab + CHOP (R-CHOP) [5]. However, to our knowledge there are no reported cases or recommendations for the treatment of localized residual mass post rituximab of PTLD. We herein describe such a case detailing presentation, therapy and long–term outcome.

2. Case presentation

A 41-year-old female with functioning renal transplantation presented to the University of Alberta Hospital (2004) with increasing diffuse abdominal discomfort, nausea, vomiting, and a palpable abdominal mass. General surgery and the transplant service (urology and nephrology) were consulted.

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http://dx.doi.org/10.1016/j.ijscr.2017.07.003

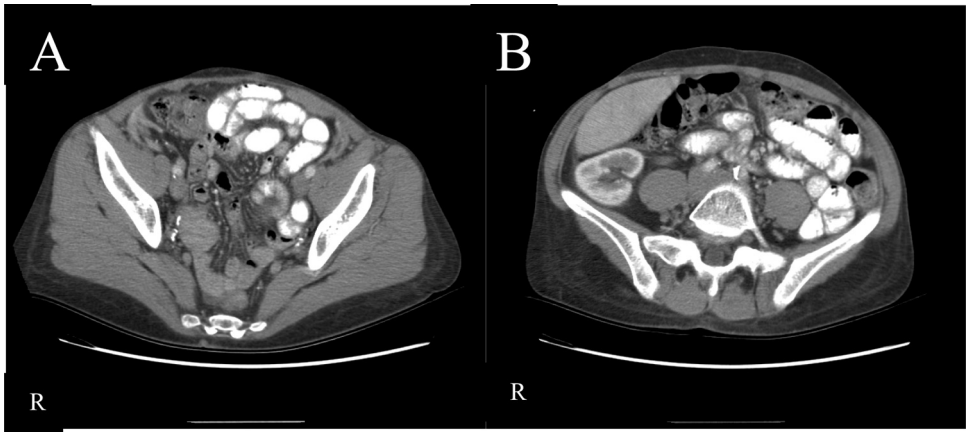

Fig. 1. An enhances CTscan of the two right sided renal transplants. The patient had an extensive transplant history with both a **(A) Right Iliac Transplant** and a **(B) Right Retroperitoneal Transplant**. Her last transplantation was in 2002 when she received a left sided iliac transplant after a prior left iliac transplant nephrectomy. Both the right sided allografts were non-functional at the time of transplantation in 2002.

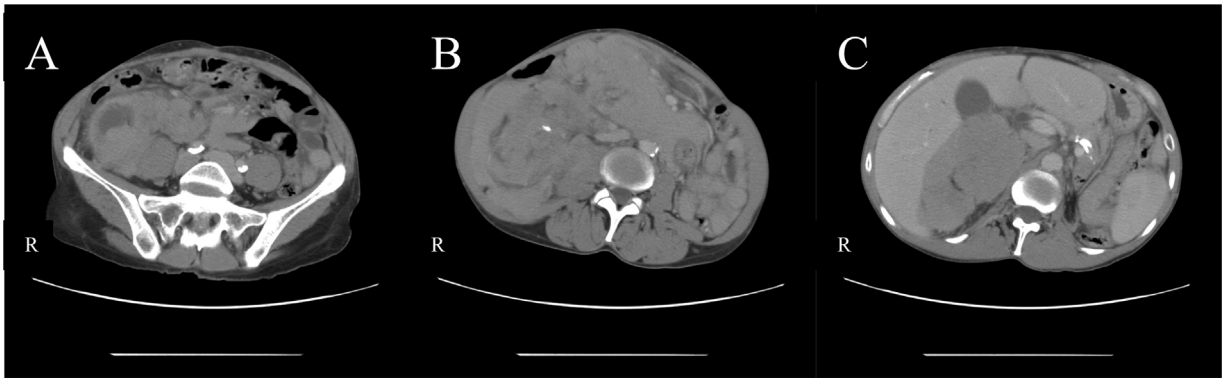

Fig. 2. A contrast enhanced CT scan of the patient's abdomen at the time of presentation. The mass was found to measure 13 × 13 × 19 cm on the right side of the abdomen. **(A) Lower Retroperitoneal Mass:** There is demonstrated involvement of a failed right-sided iliac kidney allograft. This appears grossly expanded and distorted. There are cystic regions within the mass that are most likely related to necrosis. **(B) Mid Retroperitoneal Mass:** The mass is causing soft tissue abnormalities within the retroperitoneum at the level of the duodenum and appears to involve the right retroperitoneal renal allograft. **(C) Upper Retroperitoneal Mass:** The liver is homogenous in appearance, with mild intra- and extrahepatic biliary duct dilation. There is mass effect on the pancreas with prominence of the pancreatic duct. Native right kidney is present, atrophic and does not appear to be involved by the mass.

The patient's initial end stage renal disease was of unknown etiology. She had undergone four renal transplants with the first occurring in 1979. The most recent (2002) was a living unrelated allograft placed into the left iliac fossa, with the previous left iliac fossa kidney being removed. The patient also had 2 right non-functioning cadaveric kidneys remaining in her right iliac fossa and retroperitoneum (Fig. 1). Her medical history was significant for having previously been on CellCept and Tacrolimus, and currently on Prednisone, Prograf and Trandate. She was highly sensitized and had two previous courses of OKT3 induction therapy at the time of second and third transplantations. Prior to her most recent renal transplant, she was EBV and CMV positive while the donor was EBV and CMV negative.

The patient was admitted to hospital for further management. A contrast enhanced CT scan revealed a large right sided lower abdominal mass which crossed the midline, and was associated with paracaval lymphadenopathy (Fig. 2). The huge conglomerate of masses in the retroperitoneum measured 13 × 13 × 19 cm in maximum anterior posterior (AP), transverse and craniocaudal dimensions and had cystic areas, likely related to necrosis. The masses appeared to involve the transplanted kidneys in the right retroperitoneum. The fourth transplant kidney in the left iliac fossa appeared morphologically normal. The atrophic native kidneys appeared otherwise normal. There was a mass effect on the pancreas and liver causing mild pancreatic duct, and intra and extrahepatic duct dilation. The overall bowel pattern was unremarkable.

An ultrasound guided biopsy of the abdominal mass was performed on the day of admission. The biopsies revealed large cell B cell lymphoma (CD20 positive IHC). Interestingly her EBV viral load was negative. Hematological oncology was consulted and immunosuppression was reduced to single agent Tacrolimus with a target level of 5ug/L. The patient was treated with ritixumab (four weekly 375 mg/m^2). After 4 cycles of therapy the patient underwent a follow-up CT scan of the abdomen and pelvis revealing marked improvement with significant regression of the mass which now measured 8.1 × 7.1 cm in maximum AP and transverse dimensions (Fig. 3). The largest mass persisted in the right retroperitoneum in the region of the previously transplanted kidney, and was felt to be consistent with residual PTLD. Urology was consulted to determine whether resection of the residual mass would be appropriate.

After 4 more cycles of ritixumab the patient underwent another repeat CT scan of the chest, abdomen and pelvis (Fig. 4). There was significant improvement of the retroperitoneal tumors and the two failed renal transplants in the right flank with large tumors associated with them had markedly regressed. The AP, transverse and cradiocaudal dimensions were approximately 7.0 × 7.0 × 10 cm. There were a few additional solid lesions at the medial aspect of these transplant kidneys, which had also markedly regressed, representing residual disease in enlarged lymph nodes (Fig. 5).

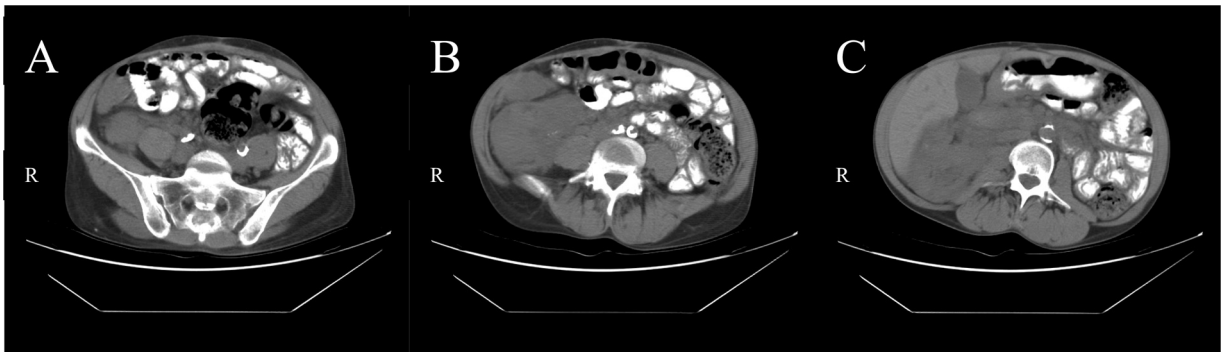

Fig. 3. A non- enhanced serial CT scan of the patient's abdomen after 4 cycles of rituxumab. Marked improvement in the appearance of the abdomen had occurred since the previous examination (see Fig. 2). **(A): Lower Retroperitoneal Mass:** An atrophic transplanted kidney is again identified. There is residual soft mass in the right retroperitoneum that is significantly smaller than at the time of presentation. The left-sided iliac fossa renal transplant appears to be functioning well. **(B): Mid Retroperitoneal Mass:** Bifurcated vessels are apparent within the mid portion of the retroperitoneal mass involving the retroperitoneal transplanted kidney above the right iliac transplanted kidney. Soft-tissue abnormalities appear to be significantly improved, with no obvious apparent lymphadenopathy. **(C): Upper Retroperitoneal Mass:** The liver demonstrates diffuse increased attenuation consistent with increased iron deposition, reflecting possible hemosiderosis. The native kidney is displaced by the retroperitoneal mass involving the retroperitoneal placed renal allograft.

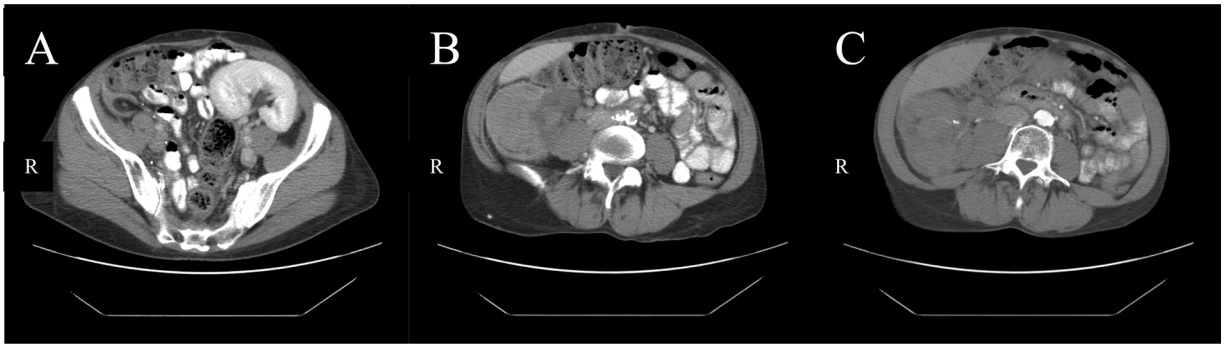

Fig. 4. A contrast enhanced CT of the patient's abdomen after completing an 8 cycle course of ritixumab. Marked improvement in the appearance of the abdomen has occurred since initial presentation (see Fig. 2) but with ongoing, persistent residual tumor. **(A): Lower Retroperitoneal Mass:** The previously failed right iliac renal allograft is present along with the functioning normal left iliac allograft. The size of the right iliac allograft is smaller than previous scan done at the time of presentation (see Fig. 2). **(B): Mid Retroperitoneal Mass:** The right retroperitoneal allograft is slightly smaller in size measuring 7.0 × 7.0 × 10.0 cm with persistent psoas mass and paracaval lymphadenopathy. **(C): Upper Retroperitoneal Mass:** Right retroperitonal allograft with decreased mass effect on the adjacent abdominal organs is observed.

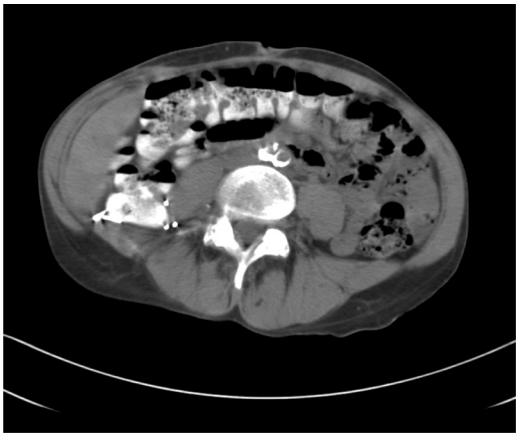

Fig. 5. A non-enhanced CT scan of the patient's abdomen post resection. The right retroperitoneal masses have been cleared along with the psoas mass and paracaval lymphadenopathy. The patient has remained disease free with good renal allograft function since being treated with ritixumab, surgery and then CHOP chemotherapy.

Because of the persistent localized masses after 8 cycles of ritixumab we elected consolidative surgical excision of the residual masses prior to pursuing cytotoxic chemotherapy with its associated toxicity and risk of infectious mortality of 31% [6]. The patient underwent surgical removal of the two prior failed allografts in the right retroperitoneum and iliac fossa, the right native kidney, and a right retroperitoneal lymph node dissection (paracaval and interaorocaval). Her operative and perioperative course were uncomplicated (LOS 5 days).

Histopathology of the resected tissue revealed large-cell B-cell lymphoma involving the third (1993) renal allograft. There was also large-cell B-cell lymphoma involving the paracaval lymph nodes, with invasion directly into the psoas muscle that had been resected with the mass.

A follow-up PET/CT scan was performed post-operatively which showed resolution of the disease on the right side, but a new questionable lesion on the left side. A repeat PET scan was performed 3 months later which demonstrated recurrence of the disease in the right abdomen and retroperitoneaum, and an increase in size of the abnormality on the left abdomen. The patient was treated with 6 rounds of R-CHOP. Upon completion of chemotherapy, the patient had a PET scan with no evidence of recurrence. No further therapy was administered and the patient was actively followed in the renal transplant surveillance clinic, and by hematologic oncology. In most recent follow-up (2017), the patient remains disease free with good function of the 4th renal allograft (GFR 60 ml/min).

3. Discussion

Surgical management alone is rarely the sole modality for treatment of PTLD. At the time of presentation (2004) a review of the literature found limited data on surgical resection for PTLD [7].

In the data we did find there was a survival advantage in those that received surgical therapy and a recommendation to cytotoxic chemotherapy [8]· In re-reviewing the literature we found descriptions of debulking surgery in the Israel Penn International Transplant Tumor Registry [9] In addition, we found descriptions of surgery for gastrointestinal related complications and with surgery these patients did well [10].

Planned consolidative surgical resection of residual mass post ritixumab for PTLD however is not described. In our case the patient demonstrated good response to ritixumab, with limited toxicity, rendering the mass resectable. The pathology of the resected residual mass revealed viable large-cell B-cell lymphoma. Despite IR it progressed, requiring salvage chemotherapy. The approach taken here was not unlike resection (salvage lymphadencectomy) of residual masses post-chemotherapy for testicular cancer. In this particular case it was felt that it would guide further therapy, and it helped space and reduce chemotherapy in a protractedly immune suppressed patient. Further reports and series of PTLD residual mass post ritixumab are needed. In particular, late outcomes of adjuvant radiotherapy toxicity are lacking in this patient population; but again extracting from the testicular seminoma data the late toxicity could be significant [11]· Our experience in this case demonstrates the potential therapeutic benefit at disease debulking allowing identification of residual disease and subsequent less intense curative chemotherapy. With the improved survival of transplant patients minimizing toxicity is an important strategy.

Conflicts of interest

There is no conflict of interest to be declared.

Funding sources

No external funding sources.

Ethics approval

As this is a Case-report study; as such no Institutional ethic approval is required. However, Informed consent for the publication of this work has been taken by the patient.

Consent

Informed consent for the publication of this work has been taken by the patient. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contributions

Conceived the concepts: RBM. Analysed the data: TDS, NZ, RBM. Wrote the first draft of the manuscript: TDS. Contributed to the writing of the manuscript: NZ, RBM. Agree with manuscript results and conclusions: TDS, NZ, RBM. Jointly developed the structure and arguments for the paper: TDS, NZ, RBM. Made critical revisions and approved final version: RBM. All authors reviewed and approved of the final manuscript.

Guarantor

Troy D. Schultz, Ronald Moore.

Acknowledgements

No acknowledgements.

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