Autologous stem cell transplantation in EBV-positive post-renal transplant refractory multiple myeloma: A case report and literature review

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Received April 30, 2016; Accepted April 7, 2017

DOI: 10.3892/ol.2018.8237

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Key words: autologous stem cell transplantation, multiple myeloma, renal transplant, lenalidomide, refractory

Abstract. Renal transplant recipients exhibit an increased risk of developing plasma cell neoplasms (PCNs; comprising multiple myeloma and plasmacytoma); however, multiple myeloma manifesting with refractory extramedullary plasmacytomas associated with Epstein-Barr virus are markedly rare in these patients. In the present case report, an unusual case of refractory multiple myeloma with multiple extramedullary plasmacytoma (including liver, vertebrae, breast, muscle, skin and soft tissues) was presented. The patient exhibited mild bone marrow infiltration which was successfully treated with novel agents, including bortezomib and lenalidomide, followed by autologous stem cell transplantation (ASCT). In addition, the patient was a renal transplant recipient who achieved a partial clinical remission with controllable therapy-related toxicity effects. Therefore, the present case indicated that ASCT is an effective and safe salvage therapy for renal transplant recipients.

Introduction

Allograft transplant patients exhibit an increased risk of developing polyclonal or monoclonal lymphoproliferative disorders, compared with the general population, due to the persistent intake of an immunosuppressant, and incidence increases with time following transplantation (1). The majority of these clonal lesions retain certain histological vestiges of a reactive condition, which suggests that the lesions may represent an early form of developed plasma cell malignancies (2). Post-transplant lymphoproliferative disorders are infected de novo by Epstein-Barr virus (EBV) through the transplanted kidney which may present early or late, be nodal or extranodal, be polymorphic or monomorphic, and run an indolent or aggressive clinical course (3). In contrast with the classical post-transplant lymphoproliferative disorders, plasma cell neoplasms (PCNs; comprising multiple myeloma and plasmacytoma), which occur following solid organ transplantation, have received relatively limited attention. Multiple myeloma (MM) represents ≤4% of all post-transplantation lymphoproliferative disorders (4), and is associated with a poor response to discontinuation of immunosuppression and conventional therapy, and a short median survival (5). MM or extramedullary plasmacytomas have been identified in post-renal transplant recipients (6) and, typically, the presence of plasma cells in the liver is associated with a more aggressive form of MM (7,8). The present case report focuses on a patient with MM who recurrently developed post-transplant EBV-associated multiple extramedullary plasmacytomas (including left scapula, liver, vertebrae, breast, skin, muscle and soft tissues) 11 years after renal transplantation. The patient was successfully treated by, and well-tolerated, a combined lenalidomide regimen followed by an autologous stem cell transplantation (ASCT).

Case report

A 45-year-old female was admitted to The First People's Hospital of Changzhou (Changzhou, China) with left shoulder pain in February 2012. Early in November 2001, the patient received a cadaveric kidney transplantation for uremia and was administered the immunosuppressives cyclosporine, azathioprine and prednisone, in a dose-tapering manner. After 2 years, the patient received cyclosporine only. In March 2008, the patient developed extramedullary plasmacytoma localized in the left nasal cavity and immunohistochemical examination of biopsy tissue was performed. Immunohistochemical
staining was performed using the EnVision method (9). Primary antibodies for AE1/AE3 (cat. no. 170308049b), CD79α (cat. no. 161122552E, clone sp18), EMA (cat. no. 16391310, clone E29), CD20 (cat. no. 170124020a, clone MX003), CD3 (cat. no. 16907545f, clone sp7), CD45RO (cat. no. 161207593h, clone uch1-1), CD138 (cat. no. 16104200E, clone M115) and Ki-67 (cat. no. 17A11203, clone MX006) [all Fuzhou Maxim (Maixin) Biotech Co., Ltd., Fuzhou, China] diluted with antibody diluent (cat. no. ab64211; Abcam, Cambridge, MA, USA) at the titer of 1:50 were used in the present study. Diaminobenzidinetetrahydrochloride (cat. no. DAB-0031) solution were provided by Fuzhou Maxim (Maixin) Biotech Co., Ltd. All samples were fixed in formalin solution and embedded in paraffin. Sections (3-4 μm) were de-paraffinized in xylene, dehydrated in ethanol, and incubated in 3% H₂O₂ for 15 min to destroy the activity of endogenous peroxidase. Following incubation at 4°C in 10% normal bovine serum (Hangzhou Bori Technology Co., Ltd., Hangzhou, China) for 10 min to block membranes, each slide was incubated with the primary antibodies at 4°C overnight. Biotin-labeled mouse anti-rabbit immunoglobulin (cat. no. BM2004; Boster Biological Technology, Pleasanton, CA, USA) was chosen as the secondary antibody. The positive and negative controls were provided by the manufacturer. Immunohistochemical analysis by two pathologists using a light microscope (Olympus Corporation, Tokyo, Japan) revealed the following: Cluster of differentiation (CD)79α, vimentin, 50% of Ki-67, epithelial membrane antigen (EMA), antibodies AE1/AE3, CD20, CD3, CD45RO and CD138 partial. Usually, 10 randomly selected microscopic fields (magnification, x100) were observed, and images were captured and analyzed using Image-Pro Plus software version 14 (Media Cybernetics, Inc., Rockville, MD, USA), using the following formula: Mean OD = sum of total integrity OD/total area. Bone marrow examination identified no abnormal plasmocytes and the X-ray revealed no bone lesion. The patient was diagnosed with isolated plasmacytoma, thus cyclosporine was discontinued and the patient was administered ramapycin (2 mg daily) and mycophenolate mofetil (1 mg twice daily), to prevent renal rejection. Between 26 March and 14 May 2008, the patient received local radiotherapy in the bilateral nasal cavity, ethmoid sinus and maxillary sinus with a total dose of 48 Gy. The following periodical examination identified normal renal function.

In February 2012, the patient began to experience left shoulder pain of an unknown cause and the following computed tomography (CT) scan revealed bone destruction of the left scapula, reactive bone formation at the 10th rib on the right side. A subsequent positron emission tomography (PET)-CT scan revealed increased metabolism of 18-fluorodeoxyglucose a standardized uptake value (SUV) of 5.5 at the left scapula with bone destruction. Subsequently, the patient underwent left scapula mass biopsy and postoperative pathological examination suggested plasma cell myeloma with immunohistochemistry results of CD20, part of CD79α, CD3, CD38, CD138, EMA, multiple myeloma oncogene 1 (MUM-1), EBV-encoded small RNAs (EBERs) and <5% of Ki-67. A bone marrow smear revealed 2% of mature plasma cells with a normal female chromosome karyotype. Interphase fluorescence chromosomal in situ hybridization (FISH) (10) of bone marrow cells identified Igλ21, retino­blastoma protein 1, p53, D1S319 and immunoglobulin (Ig) H gene abnormalities. Serum IgG concentration was 43.8 g/l and λ-light chain was 4,930 mg/dl, and serum protein electrophoresis revealed a monoclonal spike in the γ-globulin region. Urine electrophoresis revealed no monoclonal spike. Serum immunofixation electrophoresis confirmed an IgG-λ chain monoclonal M component. The hemoglobin level, serum albumin, calcium, β₂-microglobulin, lactate dehydrogenase and renal function were all normal. No marked change in antibody titers (anti-cytomegalovirus, anti-EBV or anti-hepatitis B virus surface antigen) was determined. Retrospective analysis of nasal plasmacytoma in 2008 identified EBER+. Thus, the patient was diagnosed with secondary multiple myeloma IgG-λ chain type, stage I and group A (International Staging System), post-renal transplantation. The patient refused the novel agent bortezomib and received a modified VADT (vincristine at 0.4 mg on days 1-4, doxorubicin at 10 mg on days 1-4, dexamethasone at 40 mg on days 1-4 and thalidomide at 50-150 mg on days 1-28, every 28 days) regimen for 3 cycles.

In June 2012, the patient was diagnosed as being in complete remission with negative serum immunofixation electrophoresis characterized by no monoclonal protein, as described previously (11), only 2% of mature plasma cells in a bone marrow smear and no hypercalcemia, renal failure or anemia. Subsequently, the patient received a fourth cycle of VADT regimen, followed by 3 cycles of the TD regimen (thalidomide at 100 mg on days 1-28 and dexamethasone at 40 mg on days 1-4, with 28 days/cycle) for maintenance therapy. During the period of chemotherapy, the patient was administered a decreased dose of immunosuppressive therapy (rapamycin at 2 mg daily and mycophenolate mofetil at 1 g twice daily, tapered to 0.5 g twice daily), and followed by monthly urinalysis and analysis of blood urea nitrogen, creatinine, serum IgG and light chains.

In March 2013, on routine follow-up, the patient was observed to have an increased serum IgG level (28 g/l), confirmed with M protein using serum immunofixation electrophoresis (11), suggesting an asymptomatic relapse of MM. The patient refused to receive novel agents, including bortezomib or lenalidomide, but accepted VADT regimen, as aforementioned, for 3 cycles. However, the patient's condition deteriorated gradually and, in June 2013, serum IgG increased to 57 g/l with positive serum immunofixation electrophoresis, indicating that the VADT regimen was no longer effective. Re-examination of plasma EBVDNA remained negative, suggesting no EBV viremia. Therefore, novel agents were administered for rescue therapy.

On 26 July, 23 August, 19 September and 25 October 2013, the patient received the CyB or DT regimen (cyclophosphamide at 300 mg/m² on days 1 and 8, bortezomib at 1.3 mg/m² on days 1, 4, 8 and 11, dexamethasone at 20 mg on days 1, 2, 4, 5, 8, 9, 11 and 12, and thalidomide at 100 mg on days 1-21) for 4 cycles. The subsequent evaluation revealed negative serum immunofixation electrophoresis with normal IgG levels and no abnormal plasma cells in bone marrow smear so the patient achieved a second clinical complete remission. The patient selected the TD regimen, rather thanbortezomib, for maintenance therapy and received monthly routine laboratory investigations, including ultrasonography of the abdomen.
However, 3 months later, in early February 2014, the patient began to experience a fever (temperature, 38.7˚C) with the onset of fatigue, progressive lumbago and a non-tender skin mass of the submaxilla. The following abdominal ultrasound identified a diffused hypoechoic lesion (maximum diameter, 8.0x6.5 cm) in the liver. A full blood count revealed: Hemoglobin, 84 g/l; hematocrit, 35.6%; mean corpuscular volume, 86 fl; white blood cells, 8.79x10⁹ cells/l; and platelets, 134x10⁹ cells/l. Liver function tests were in the normal range. The total protein serum level was 28 g/l and the protein electrophoresis revealed the presence of a monoclonal band in the gamma region, which was identified as IgG-λ using immunofixation. Viral markers for hepatitis C and hepatitis B virus were negative. Neither serum anti-EBV antibody nor plasma EBV-DNA was detectable. An upper abdominal CT scan revealed that multiple round-like and well-defined lesions, of various sizes, with low attenuations were present in hepatic parenchyma. Following intravenous injection of meglumine diatrizoate contrast media, the enhancements of lesions were mild and heterogeneous. These results were considered to be caused by myeloma (Fig. 1). Magnetic resonance imaging (MRI) fat suppression T2WI (12) identified soft mass and multiple patchy lesions with high attenuations in T12 thoracic and L1-L4 lumbar vertebrae. The soft tissue surrounding S1 and S2 was swollen (Fig. 2). Therefore, a CT-guided percutaneous needle biopsy of the hepatic lesion was performed and the subsequent histological study (hematoxylin and eosin stain) revealed diffused viability of plasma cells. The immunohistochemical examination revealed CD20+, CD3+, CD38+, CD138+, IgG-κ<IGG-λ+, MUM-1+, between 30 and 40% Ki67+, and EBV-encoded RNA+, indicating extramedullary
liver plasmacytoma (Fig. 3). Bone marrow aspirate identified 6% plasma cell infiltration and CD138 sorting interphase FISH of bone marrow cells revealed 1q21 amplification. Serum IgG was 62 g/l and was confirmed with M protein using serum immunofixation electrophoresis.

The patient experienced rapid relapse 3 months after the CyB or D regimen and therefore accepted the RCd regimen (lenalidomide at 25 mg on days 1-21, cyclophosphamide at 50 mg on days 1-21, dexamethasone at 20 mg on days 1, 8, 15 and 22, with 28 days/cycle) and discontinued the immunosuppressant. Re-evaluation demonstrated that serum IgG decreased to 27 g/l and ultrasonography revealed that the hepatic mass decreased in size to 6.8x5.5 cm, indicating that extramedullary liver plasmacytoma was sensitive to the RCd regimen.

The patient continued the third and fourth cycle of the RCd regimen and the following upper abdominal CT scan revealed that the extramedullary liver plasmacytoma decreased (1 July 2014; Fig. 1C and D). The hemoglobin level was 114 g/l and serum IgG was 13.6 g/l. During the fourth cycle of the RCd regimen, the patient experienced transient agranulocytosis with pulmonary infection. The patient exhibited no fever or lumbago following treatment for the infection and recovery of myelosuppression, indicating that the patient exhibited good partial remission, following four cycles of the RCd regimen.

The fifth cycle was subsequently administered. The following abdominal CT (25 August 2014) demonstrated further decreased size of extramedullary liver plasmacytoma (Fig. 1E and F) and a lumbar vertebral MRI (26 August 2014) identified a decrease in soft tissue mass in T12 and alleviated swelling of soft tissue surrounding S1 and S2 (Fig. 2B). The patient was under outpatient follow-up and accepted the RCd regimen for maintenance therapy from September 2014, exhibiting a good response and stable disease, with the exception of controllable myelosuppression. However, the patient’s condition deteriorated from 4 December 2014 with the manifestation of progressively enlarged, hard right breast lump (diameter between 7.7x8.5 and 9.6x10.2 cm), detected using ultrasonography (Fig. 4A and B). The following biopsy revealed plasmacytoma with similar immunohistochemistry results: CD38+, CD138+, IgG-k< IgG-λ, MUM-1+, with the exception of 80% Ki-67+, which was increased compared with liver plasmacytoma (Fig. 4C). At this time, the patient had received 6.5 courses of the RCd regimen and bone marrow examination revealed no evidence of bone marrow infiltration. Thus, ASCT was subsequently carried out. On 19 December 2014, when absolute neutrophil count <0.5x10^9 cells/l, the patient was mobilized with etoposide (1.6 g/m^2) intravenously, followed by granulocyte colony-stimulating factor (G-CSF; 10 µg/kg/day; Jilifen, China) and this continued until leukapheresis was completed. The total number of mononuclear cells collected was 11.33x10^8 cells/kg and a total of 12.68x10^6 cells/kg CD34+ cells were collected. However, a CT scan revealed that the right breast plasmacytoma remained the same size which suggested that it was resistant to a high dose of etoposide chemotherapy (Fig. 4D). An abdominal CT scan identified a mild lesion in the liver.

Between 19 January and 2 March 2015, the patient received radiotherapy of planning target volume (PTV) at 5, 035.8cGy/25 fractions (fx) for right breast plasmacytoma and 95% PTV at 4,500.8cGy/25fx for right breast. During radiotherapy, the patient experienced IV grade myelosuppression which resulted in delayed radiotherapy and gradually worsening right hip pain. An MRI scan (28 February 2015) of the hip revealed an abnormal signal of bilateral femur neck, middle-upper part of the femur, iliac bone and right internal iliac muscle, indicating myeloma-associated bone disease and extramedullary plasmacytoma. The patient received palliative supportive therapy until mid-May 2015 due to severe myelosuppression with a progressively increased IgG level,
aggravated right hip pain and enlarged internal iliac muscle lump. The IgG level increased to 38.9 g/l, the right internal iliac muscle lump enlarged to 12 cm in diameter (Fig. 5A). Plasma EBV DNA remained undetectable, indicating no EBV viremia. The patient experienced unbearable pain and was unable to lie down. The patient elected to receive ASCT as the final salvage therapy. Following provision of written informed consent, stem cells were infused on day 0 and the patient was administered a conditioning regimen of a high dose of melphalan (200 mg/m$^2$) on day 2. The patient received subcutaneous G-CSF (10 µg/kg) from day 3 of ASCT for 3 consecutive days, until the neutrophil counts were $>1.0 \times 10^9$ cells/l. Prophylaxis for opportunistic infections and antimicrobial therapy in cases of febrile episodes were administered, according to the Chinese guideline for the clinical application of antibacterial drugs for agranulocytosis with fever (13). The patient reached an absolute neutrophil count of $>0.5 \times 10^9$ cells/l on day 13 following infusion of stem cells, however, the platelet count was persistently $<20 \times 10^9$ cells with intermittent platelet transfusion twice a week for ~2 months. During the transplantation, dynamic detection of the liver and renal function was normal, despite stopping immunosuppressants, the hip pain relieved from day 1 and the enlarged lump of the right hip was non-palpable. After 2 months, an MRI revealed improvement of the right hip, compared with those of the pre-transplantation (Fig. 5B).
The patient received MPR (melphalan, prednisone and lenalidomide) as maintained therapy and periodical platelet transfusion if platelet counts were <20x10⁹ cells/l.

The patient remained relatively stable until October 2015. The patient experienced a rapid relapse of right neck soft tissue plasmacytoma which progressively enlarged from mid-October 2015 (Fig. 5C). Therefore, the patient was administered decitabine (20 mg/m² for 5 days) as an experimental treatment. However, the condition deteriorated during myelosuppression and the patient succumbed to pulmonary infection in mid-November 2015, following a prolonged survival of 6 months from salvage ASCT.

Discussion

The number of solid organ transplant recipients continues to increase, therefore it is hypothesized that the cases of post-transplant lymphoproliferative disorder (PTLD) will also increase. PTLD represents a heterogeneous group of lymphoproliferative processes associated with the immunosuppression in transplant recipients (4,14). It is a potentially life-threatening complication of organ transplantation which affects between 3 and 20% of solid organ transplant recipients (4,15) and the incidence of PTLD in transplant recipients is increased between 30- and 50-fold, compared with that of the general population (16). Risk factors for PTLD include degree and length of immunosuppression, recipient's EBV infection status and type of organ transplant (4,17). The median time for PTLD diagnosis was between 5 and 7 years following transplantation (18). According to the World Health Organization Classification, PTLD is characterized into four groups as follows: Early lesions, polymorphic PTLD, monomorphic PTLD and classical non-Hodgkin's lymphoma type PTLD (19).

Plasmacytoid PTLD is a rare type of PTLD, with an incidence of <4% of PTLD cases (20), and there are limited studies on the clinical presentation and outcome of this disease subtype. Unlike traditional multiple myeloma, which commonly involves the bone marrow only and may present with lytic boney lesions, plasmacytoid PTLD uniformly presented with plasmacytomas, which behave in a manner similar to a lymphoma with mass lesions (21). The possible contributing factors include older age recipients, a donor who was brain dead at the point of donation, onset of EBV infection post transplantation (4), hepatitis C virus infection in recipients and administration of antithymocyte/antilymphocyte globulin following solid organ transplantation (4). Post-transplant plasmacytomas have been described in the allograft, skin, peritoneum, gastrointestinal tract, gingiva and, occasionally, at other sites (21-25). To the best of our knowledge, extramedullary plasmacytoma of liver is associated with more aggressive forms of multiple myeloma and its presumptive ante mortem diagnosis is often based on clinical findings, including hepatomegaly and laboratory alterations of liver function tests (25). In patients with plasmacytoid PTLD, the predominant transplanted organs were kidneys or the heart (26). Of kidney transplant recipients, between 1 and 4% developed PTLD (27) and limited cases of extramedullary plasmacytomas have been examined in kidney transplant recipients (23). The incidence of multiple myeloma is rare in renal graft recipients, despite monoclonal gammapathies presenting in these patients post-transplantation (28). The present case report describes the identification of a rare clinical case, which met the required clinical and laboratory criteria for plasmacytoid PTLD, following renal transplantation. The patient in the present case report developed EBV-associated nasal plasmacytoma 7 years post-renal transplantation with presentation of multiple myeloma. Subsequently, after 11 years, the patient relapsed with extramedullary plasmacytoma of the liver, vertebræ, breast, muscle, skin and soft tissues. Additionally, no high frequency of abnormal plasma cells was present in bone marrow cells, which was consistent with literature reports. For the patient, deceased-donor and EBV infection were the two major contributing factors for plasmacytoid PTLD.

The mean time between PTLD diagnosis and transplantation was 129 months which suggests that long-term immunosuppression or antigen stimulation, following transplantation, may serve a role in the pathogenesis of PTLD (19). B-cell viability is considered to be induced by EBV infection in a number of PTLD cases (29), which arises in the setting of pharmacological immunosuppression, leading to impaired T-cell function and loss of control over EBV-infected cells. EBV-naive patients who receive a donor organ from an EBV-infected donor are at the highest risk of developing PTLD (30). The presence of EBV within the tumor cells of EBV-naive patients who received a donor organ from an EBV-infected donor distinguishes between plasmacytic PTLD and classical plasma cell myeloma observed in non-transplant patients where EBV is rarely present (5). Of the patients with PTLD which developed following kidney transplant, ~90% was of B-cell origin and between 90 and 95% contained EBV as a consequence of either reactivation of the dormant virus post-transplantation or acquisition from the kidney donor (20,23). In the present case report, EBV-associated multiple extramedullary plasmacytomas of the nasal cavity, left scapula, liver, vertebræ, breast, skin, muscle and soft tissues in a renal allograft recipient were examined. In this patient, nasal, scapula, liver and breast plasmacytomas were confirmed by postoperative histopathological examination or CT-guided percutaneous needle biopsy. In situ hybridization analysis of EBV-encoded RNA (EBER) was positive in the nasal cavity, scapula, liver and breast lesion, indicating that the plasmacytoid PTLD of this patient was associated with EBV infection.

There is no consensus on the optimum approach to the treatment of PTLD. The initial treatment involves immunosuppression modification (31,32), which is adequate in a number of patients; however, additional treatment including chemotherapy and antiviral therapy are required in patients with aggressive tumors (22,33). There are currently no clear guidelines for the solitary plasmacytoma therapy in renal transplant recipients, due to its rarity, and it is hypothesized that the treatment for these patients should be individualized.

For patients with eligible multiple myeloma, the treatment of choice includes induction therapy (usually involving novel biological agents) followed by ASCT (34). The CyB or D regimen is effective in multiple myeloma and produces rapid and complete hematological responses in the majority of patients (35-38). Previous case reports suggest that
lenalidomide is an effective agent in combination with dexamethasone (38,39). However, this treatment is generally not considered to be curative and relapses occur. The CyB or D regimen was administered to the patient in the present case report and a good clinical response was observed, which was consistent with previous studies (35-37).

Following the patient's third relapse with extramedullary liver plasmacytoma within 3 months, the patient was administered the RCD regimen (avoiding bortezomib resistance) combined with intermittent ganciclovir (for EBV infection) and a good partial remission was observed, suggesting that the novel immunomodulatory lenalidomide is effective for the treatment of extramedullary liver plasmacytoma. Following the patient's fourth relapse with breast, hip muscle, femur neck, skin and soft tissue plasmacytomas, local radiotherapy and subsequent ASCT, using a conditioning regimen of a high dose of melphalan, was administered and a good response was observed. This indicated that radiotherapy is an effective treatment of breast plasmacytoma and melphalan is effective at treating soft tissue plasmacytoma. Notably, the patient's liver plasmacytoma was stable following lenalidomide treatment, suggesting that distinct plasmacytoma may exhibit distinct biological features; however, further gene expression profile screening is required for validation.

The aforementioned treatments are typically not considered curative and relapses occur. It is hypothesized that an allo- or non-myeloablative hematopoietic stem cell transplantation or novel agents may be considered for patients with plasmacytoid PTLD. Additional studies are required to identify correct management of this condition.

The present case report demonstrates an unusual form of plasmacytoid PTLD, distinguished by its involvement of multiple extramedullary sites, stable liver plasmacytoma situation and multiple times of disease relapse, and novel curative regimens, including newer biological agents and ASCT. The present case report identifies areas of required investigating including the pathogenesis, the clinical behavior and the appropriate treatment of post-transplant extramedullary plasmacytoma. Notably, the present case report identifies ASCT as a valuable, feasible and well-tolerated treatment for post-rental transplant patients with refractory multiple myeloma. Additional clinical studies are required to further elucidate and validate these hypotheses.

Acknowledgements

The authors thank Dr Changqing Lu and Dr Tongbin Chen (The First People's Hospital of Changzhou, Changzhou, China) for their assistance with the pathological analyses, and Dr Jun Sun (The First People's Hospital of Changzhou) for his assistance with radiological analyses.

Funding

The present case report was supported by the Fund of Science and Technology Bureau of Changzhou, Jiangsu, China (grant nos. CJ20130035 and CJ20150418), the Changzhou High-Level Medical Talents Training Project (grant no. 2016ZCLJ024) and the Fund of 333 Project of Jiangsu Province, China (grant no. BRA2015088).

Availability of data and materials

All datasets generated and analysed in the present study are included in this published article.

Authors' contributions

XX, WG conceived and designed the study. YL, YC, WD, WW, YZ, DL, HL and WG performed all the clinical diagnosis and treatment. QL performed the pathological detection. YL and YC analyzed the data. XX and YL wrote the manuscript. WG revised the manuscript. All authors have read and approved the final manuscript.

Ethics and consent to participate

This study was approved by the Ethic Committee of the First People's Hospital of Changzhou, and the written informed consent was gained from all participants.

Consent for publication

All the study participants provided consent for the data to be published.

Competing interests

The authors declare that they have no competing interests.

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