Very late-onset EBV-related cutaneous post-transplant lymphoproliferative disorder

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SUMMARY

The Epstein-Barr Virus-related cutaneous post-transplant lymphoproliferative disorder (EBV-cPTLD) is an exceptional complication of the immediate post-transplant period, related to the immunosuppression leading to EBV reactivation. EBV-cPTLD presents a heterogeneous dermatological spectrum complicating the diagnosis, hence requiring histology, immunohistochemistry (IHC) and in situ hybridisation (ISH) for confirmation.

A woman in her 70s with a 24 year history of renal transplantation presented atypical infiltrated, hyperpigmented lesions on the left arm and leg along with general health deterioration. Histology, IHC and ISH on skin biopsy demonstrated an EBV-positive infiltration, confirming plasmablastic lymphoma, a form of EBV-cPTLD. A Positron Emission Tomography/Computed Tomography (PET/CT) demonstrated hypermetabolic cutaneous and bone infiltrations that resolved after an rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone treatment.

This case illustrates that cPTLD should be included in the differential diagnosis of atypical skin lesions, even decades after transplantation. Although retrieving EBV in late cPTLD is exceptional, this case shows that proliferating EBV can be demonstrated in very late-onset cPTLD.

BACKGROUND

The Epstein-Barr Virus (EBV) is part of the g-Herpesviridae and linked to various cutaneous manifestations, particularly affecting the immunocompromised host.[1–3] EBV affects around 90% of the population and establishes a latent infection in B-cells which are under the control of cytotoxic T-cells, avoiding proliferation of EBV. The immunosuppressive treatment post-transplantation impairs many T-cell functions, hence permitting uncontrolled EBV-driven B-cell proliferation, through Epstein-Barr Nuclear Antigen (EBNA) and Latent Membrane Protein 1 (LMP1) viral protein expression.[4 5]

Post-transplant lymphoproliferative disorders (PTLD) involve T, B-cell or NK cell proliferation in an immunosuppressed organ transplant recipient.[6] PTLD is frequently associated with EBV and is categorised in six entities, including three non-destructive PTLDs (florid follicular hyperplasia, mononucleosis-like lesions and plasmocytic hyperplasia), monomorphic PTLD, polymorphic PTLD and classic Hodgkin's lymphoma-like PTLD.[7]

The frequency of PTLD varies between 1% and 20% of the transplant recipients and depends on the type of transplant, the severity of the immunosuppression, as well as the EBV status. Renal transplant recipients are less often affected compared with intestinal, heart and lung transplant recipients.[4 8] Cutaneous PTLD (cPTLD) represents about 5%–10% of all PTLD cases. EBV-related cutaneous post-transplant lymphoproliferative disorders (EBV-cPTLD) is most common in the early (<1–3 years) post-transplant period, occasionally observed in the late (1–10 years) post-transplant period, but very late onset is exceptional (>10 years).[9 10]

cPTLD may resemble various dermatoses,[11 12] including non-specific nasal ulcerations,[13] subcutaneous nodules, ulcerations, plasmocytoma,[14] plasmablastic lymphoma (PBL)[15] and extranodal NK/T-Cell lymphoma.[16]

The EBV-cPTLD are linked to the reactivation and proliferation of the EBV virus in the context of the early post-transplant period when severe iatrogenic immunosuppression is required.[5]

This case report presents a patient with a very late onset of EBV-cPTLD, 24 years after renal grafting.

CASE PRESENTATION

A woman in her early 70s underwent renal transplantation in 2000 for renal polycystosis, 3 years after the initiation of haemodialysis. Her current medication included: methylprednisolone 4 mg/d, tacrolimus 2 mg/d, olmesartan 40 mg/d, nebivolol 5 mg/d, lercanidipine 20 mg/d, moxonidine 0.4 mg/d, furosemide 40 mg 1d/2, atorvastatine/ezetimibe 10 mg/40 mg 1x/d, acetylsalicylicum 80 mg/d, calcium carbonate 1 gr/d, L-thyroxine 75 microgr/d, paroxetine 20 mg/d, linagliptine 5 mg/d, denosumab 1/6 months, pantoprazole 40 mg/d, allopurinol 300 mg ½/d and furadantine 100 mg/d. The immunosuppressive regimen treatment remained identical for the last 10 years. Regular bladder infections were noted.

Twenty-four years after the renal transplantation, the patient progressively developed, over a 3-month period, several asymptomatic, infiltrated, non-pruritic, carton-like lesions with a diffuse hyperpigmentation as well as an atrophic cicatricial aspect of her left arm (figure 1a) and left leg (figure 1b). She had no previous history of skin disease. The patient was hospitalised for a workup in the context of fatigue, anorexia and weight loss.

INVESTIGATIONS

Skin biopsies were performed. Histology of the cutaneous lesions was suggestive of a high-grade lymphoproliferation of the cPTLD type (figure 2a,b). The epidermis was unremarkable. In

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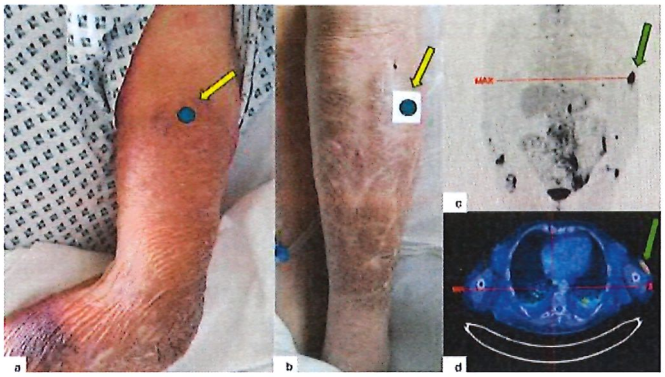

Figure 1 (a) Diffuse erythematous infiltrations of the upper arm (Yellow arrow: biopsy site), (b) Diffuse erythematous infiltrations of the leg, carton-like skin and scarring (Yellow arrow: biopsy site) and (c, d) PET/CT revealing hypermetabolic cutaneous and subcutaneous infiltrations (Green arrow: biopsy sites).

the dermis and hypodermis, a dense, diffuse infiltrate of large lymphoid cells of different sizes was evidenced. Mitoses were frequent, with an abundant cytoplasm. Some cells presented a plasmablastic/immunoblastic aspect. immunohistochemistry (IHC) demonstrated that the lymphoid cells expressed CD138 (figure 2c), MUM1 and C-Myc. These cells were negative for BCL-2, CD20, CD3, BCL-6, CD5, cyclin D1 and CD10. Ki67 was expressed in 90% of the neoplastic cells (figure 2d). In situ hybridisation (ISH) using an anti-EBER probe (INFORM, Roche Diagnostics) revealed a positive signal (figure 2e). Herpes virus type 8 immunostaining was negative. The conclusion was an EBV-cPTLD PBL.[3] A PET /CT demonstrated numerous cutaneous and subcutaneous as well as bone hypermetabolic infiltrations (figure 1c,d). A gastroscopy revealed a fibrinous ulceration of the fundus and biopsies demonstrated the same lymphomatous infiltration as observed in the skin.

OUTCOME AND FOLLOW-UP

A combined treatment with the anti-CD20 antibody rituximab and a cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy was initiated, followed by a progressive improvement of her skin lesions, but unfortunately, new skin lesions appeared 3 months later. She eventually died from her disease in the year following the diagnosis.

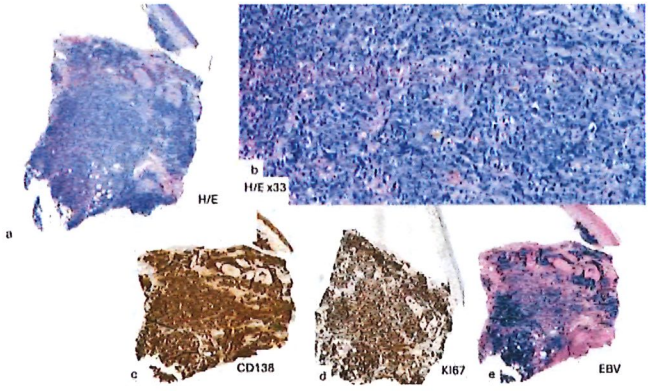

Figure 2 (a) Diffuse lymphocytic infiltration of the dermis and hypodermis (H/E x4), (b) Dense and diffuse infiltrate of large lymphoid cells in the dermis (H/E, x33), (c) Intense CD138 immunostaining (x4), (d) Ki67 immunostaining demonstrating a positive signal in 90% of the infiltrating cells, (x4) and (e) in situ hybridisation revealing a positive signal for EBV (x4). EBV, Epstein-Barr Virus.

Table 1 Epstein-Barr Virus-related muco-cutaneous manifestations

Direct EBV involvement	Indirect EBV involvement
Oral hairy leukoplakia	Ampicillin-EBV-related rash
EBV-PTLD	Erythema multiforme
NK/T-cell cutaneous lymphoma	Acute generalised exanthematous pustulosis
Langerhans cell sarcoma	Hypersensitivity to mosquito bites
Mononucleosis-associated skin rash	Gianotti Crosti
Genital ulcerations (Lipschutz's ulcer)	Unilateral thoracic exanthema
Smooth muscle cell tumours	

EBV, Epstein-Barr Virus; PTLD, post-transplant lymphoproliferative disorders.

DISCUSSION

The EBV virus is a ubiquitous DNA virus with a high seroprevalence (75%–80%), often already acquired during childhood, but rarely pathogenic in the immunocompetent host. In contrast, in the immunocompromised patient, EBV is responsible for an important array of acute and chronic mucocutaneous diseases.[17] EBV can either act through direct replication in mucosal keratinocytes, leading to oral hairy leukoplakia[16] or causing smooth muscle cell tumours,[18] genital ulcers,[19] severe mosquito bite allergy,[20] granulomatous reactions[21] or Langerhans cell sarcoma.[22] Furthermore, EBV can also lead to indirect cutaneous diseases such as Gianotti-Crosti syndrome, acute generalised exanthematous pustulosis, unilateral thoracic exanthema, Drug Reaction with Eosinophilia and systemic Symptoms (DRESS) syndrome,[23] erythema multiforme,[24] etc. Mononucleosis and the EBV-associated cutaneous rash are other examples of EBV-related dermatoses.[17 25] Table 1 resumes the different directly and indirectly EBV-associated mucocutaneous manifestations.

cPLTD usually occur in the early post-transplant period[9 10] and are regularly linked to EBV reactivation or are due to immunosuppressive agents including methotrexate[26] or TNF-alpha antagonists.[27 28] In a large, multi-centre cohort including 512 patients, 18.4% experienced EBV reactivation during the first post-transplant year,[29] while others reported 1%–10% EBV-related cPTLDs.[13] However, others described cPTLD reactions 7–8 years post liver and heart transplantation[13] and 15 years after renal transplantation.[7] Early cPTLD is, in general, EBV-related, whereas late-onset cPTLD is usually EBV-negative. However, in this very late-onset PTLD, EBV was demonstrated, potentially linked to her recurrent bladder infections.

cPTLD has multiple clinical presentations with non-specific ulcerations or infiltrating subcutaneous nodules.[7 15] Dermoscopy, by recognising salmon-coloured background lesions with sparse white structureless areas, white lines, white hairpin structures and unfocused dotted vessels, can be helpful to support a clinical suspicion, to assess treatment efficacy or for monitoring eventual recurrences.[30]

Standard histology is usually suggestive of cPTLD and ISH is the preferred technique to identify EBV in the sampled skin. Systemic EBV viral load can also be analysed. PET/CT and CT imaging techniques are helpful to stage PTLD and follow treatment response.[28]

Whereas systemic PTLD is often associated with a poor prognosis, cPTLD usually responds positively to treatment.[7 13]

The first step of the management of PTLD is to opt for immunosuppression reduction, guided by the transplant team while monitoring graft function.[31] If this option fails, according

to the clinical severity, rituximab anti-CD20 therapy (four weekly infusions) is indicated, followed or not by a CHOP (four cycles) chemotherapy. In very high-risk patients (thoracic organ transplant and disease progression following four cycles of SC rituximab monotherapy), six cycles of chemoimmunotherapy (R-CHOP alternating with DHAO-X) could be recommended.[31] EBV-specific cytotoxic T lymphocyte therapy and autologous haematopoietic stem cell transplantation remain therapeutic alternatives in the event of the failure of the first-line options.[24 25 27 31 32] For more limited cPTLD, surgery or radiotherapy could also be considered.

In conclusion, in the event of the progressive appearance of atypical cutaneous manifestations, even decades after organ transplantation, the diagnosis of EBV-cPTLD should always be considered. Histology, IHC and EBV-ISH are mandatory for the final diagnosis.

Learning points

- Cutaneous post-transplant lymphoproliferative disorders (cPTLD) are exceptional.
- Clinical presentations of cPTLD are highly heterogeneous.
- Early cPTLD is usually linked to Epstein-Barr Virus (EBV) and observed during the immediate post-transplant period due to severe iatrogenic immunosuppression, whereas late cPTLD is commonly EBV-negative.
- Very late onset cPTLD should always be kept in mind in grafted patients, even decades after transplantation, and EBV can still be incriminated.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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