CASE REPORT

The development of peripheral T-cell lymphoma after successful treatment for diffuse large B-cell lymphoma in a patient with suspected adult onset immunodeficiency: more questions than answers?

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SUMMARY

We present the case of a 60-year-old woman who developed peripheral T-cell lymphoma following successful treatment for high-grade B-cell non-Hodgkin's lymphoma. We consider the possible aetiology of this unusual occurrence. We hypothesise that this case represents one of the undiagnosed adult-onset immunodeficiency, in which the pathogenesis of the patient's T-cell lymphoma may have been in part iatrogenic, namely related to previous immunotherapy with rituximab. We feel this case highlights the importance of rebiopsy in patients with recurrent lymphadenopathy and a history of haematological malignancy and hence acts as an important aide memoir in the investigation of such cases.

BACKGROUND

When this case arose, we felt it illustrated a rare occurrence. A literature search confirmed that a diagnosis of T-cell following B-cell lymphoma was extremely unusual outside the transplant setting. We set out to closely examine this patient's history in an effort to ascertain which, if any, of the factors in this case, led to the development of such a phenomenon.

CASE PRESENTATION

We present the case of a 60-year-old woman who developed metachronous B-cell and T-cell lymphomas during a 10-year period. The patient initially presented in 2001, aged 49, with fevers, sore throat and cervical lymphadenopathy. She had no family history of malignancy or immunodeficiency. Her only medical history was of recurrent tonsillitis requiring tonsillectomy aged 44. The histological findings were considered non-specific as detailed below. Following resolution of the lymphadenopathy she was discharged from follow-up.

In 2008, the patient presented with bilateral cervical lymphadenopathy. She was otherwise asymptomatic. Lymph node biopsy was carried out and a diagnosis of diffuse large B-cell lymphoma (DLBCL) was established. Immunochemotherapy resulted in complete radiological remission. The patient remained under haematology follow-up. In 2010, she reported of breathlessness and moderate left ventricular impairment was noted on an echocardiogram. This was attributed to anthracycline-related cardiac toxicity.

In 2011, the patient reported of enlarged neck nodes and night sweats. Investigations established a diagnosis of peripheral T-cell lymphoma, not otherwise specified (NOS).

INVESTIGATIONS

2001: Serological investigations yielded negative results for HIV 1+2 antibodies, toxoplasma IgM and IgG antibodies and syphilis antibodies. Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) IgM antibodies were negative while anamnestic IgG antibodies were both positive. Biopsies from a parotid lymph node showed preserved architecture with the expansion of the T-cell compartment, attenuation of B-zones with virtual absence of secondary lymphatic follicles, but with a well-developed follicular dendritic cell meshwork populated by small CD20/IgD B cells suggestive of primary follicles. These were surrounded and partly 'invaded' by shred-like collections of epithelioid histiocytes mixed with T-cells and occasional large CD20 B cells (figure 1A).

2008: A lymph node excision biopsy revealed changes similar in principle to the 2001 biopsy, but the population of CD20 large B cells showed increased cytological atypia and were expanded into sheets consistent with a diagnosis of DLBCL (figure 1B). Staging investigations indicated stage 3A disease.

2011: Cervical node biopsy revealed atypical medium-sized CD3/CD4/CD8- T cells, expressing aberrant immunophenotype with a loss of CD5 and CD7. B cells were represented by aggregates of small lymphocytes occupying the CD21/CD23 hyperplastic dendritic cell meshwork. No germinal centres were observed (figure 1C). Clonality studies failed to demonstrate a single clonal T-cell receptor (TCR) rearrangement, but did detect oligoclonal T-cell rearrangements on TCRγ PCR. BIOMED-2 multiplex PCR did not identify a clonal B-cell population. The findings were considered diagnostic of peripheral T-cell lymphoma, NOS. Staging investigations indicated stage 3B disease. The serum electrophoresis showed low IgG and IgM levels (3.87 and 0.27 g/L, respectively,) with normal IgA and no monoclonal band. The serum EBV PCR was negative and human T-lymphotropic virus type antibodies were not detected.

Previous biopsies were reviewed and latent membrane protein (LMP1) expression was demonstrated

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Figure 1 (A) 2001—a primary follicle (upper left), a rim epithelioid histiocytes (lower right) and an individual large-cell latent membrane protein (LMP1+; inset, $\times 600$). (B) 2008—Epstein-Barr virus+ diffuse large B-cell lymphoma composed of sheets of large cells CD20+ (right inset, $\times 400$) and LMP1+ (left inset, $\times 400$). (C) 2011—peripheral T-cell lymphoma, not otherwise specified, composed of CD3+ (inset $\times 400$) medium to large cells with high mitotic activity interspersed between numerous epithelioid histiocytes. All sections H&E, magnification $\times 400$.

in individual large B cells in 2001 lymph node biopsy as well as in DLBCL diagnosed in 2008 indicating EBV infection (figure 1B). By contrast, no LMP1 or Epstein-Barr virus—encoded RNA (EBER)-positive cells were demonstrated in the 2011 biopsy.

TREATMENT

2008: This patient's DLBCL was treated with eight cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) chemotherapy.

2011/2012: Following a multidisciplinary team discussion, the patient was started on cisplatin, cytarabine and dexamethasone (DHAP) chemotherapy, with purposeful avoidance of anthracyclines. The patient developed renal failure following the first cycle of this regimen, precluding further cisplatin use. Good partial remission at this point was consolidated with autologous stem cell transplant.

OUTCOME AND FOLLOW-UP

On completion of an autologous stem cell transplant in 2012, a positron emission tomography CT scan demonstrated a complete radiological and metabolic response. The patient remains alive and well 12 months following the diagnosis of peripheral T-cell lymphoma.

DISCUSSION

We have described a rare case of a duplex T-cell after B-cell malignant lymphoma. Only sporadic similar cases have been reported to date, of these, most developed after bone marrow or solid organ transplantation.^{1–4} In this patient, EBV DLBCL diagnosed at the age of 56 years appeared to develop from LMP1+ cells retrospectively detected in a lymph node biopsy carried out 7 years earlier. The peripheral T-cell lymphoma,

NOS, was diagnosed 3 years after achievement of complete remission following R-CHOP therapy.

This is an interesting case raising several questions: Is there a unifying pathogenic concept for all three episodes in the 10-year history? Could rituximab have contributed to the development of a metachronous T-cell lymphoma? And finally, can lymph node biopsy assist in the diagnosis of adult-onset immunodeficiency?

In recent years, physiological age-related decline in immune functions known as immune senescence has been blamed for the development of lymphoproliferative disorders of divergent biological significance, including malignant lymphoma.⁵ In 2008, the WHO classification recognised EBV+ DLBCL of the elderly (defined as over 50 years) as a diagnostic entity.⁶ The diagnosis can be made in a patient with no history of lymphoma or immunodeficiency. While, by this definition, our patient could be considered as elderly; her unexplained systemic symptoms and early histological changes in 2001 have led us to consider alternatively an undiagnosed idiopathic immunodeficiency. Indeed, common variable immunodeficiency (CVID) is usually diagnosed in the second to fourth decades and the diagnosis is often delayed.⁷ CVID is defined as a significant reduction in one of the major isotypes of immunoglobulin; onset of immunodeficiency at greater than 2 years; absent isoheamagglutinins and/or poor response to vaccines; and the exclusion of defined causes of hypogammaglobulinaemia.⁸ The clinical presentations of CVID are heterogeneous but are recognised to be associated with recurrent infections of the respiratory tract.⁷ In our patient, a history of tonsillitis and tonsillectomy at age 44 may lend possible support to the idea of CVID. Certainly, EBV+ cells in the first biopsy and the development of EBV+ DLBCL 7 years later provide an argument for underlying immunodeficiency^{5 9}; however, it is also necessary to reflect on the possible

iatrogenic role of rituximab. CD20 is not strongly expressed by plasma cells and yet several cases of hypogammaglobulinaemia following rituximab therapy have been reported.^{10–11} Indeed, we must consider the possibility that rituximab was responsible for this patient's hypogammaglobulinaemia, or may have enhanced an underlying immune defect: the hypothesised CVID and/or immune senescence-related decline in immune functions.

By contrast, a similar pathogenic link to the EBV-negative peripheral T-cell lymphoma cannot be easily established. Emergence of T-cell oligo (clones) which are usually, but not exclusively CD8, has been reported in B-cell lymphoproliferative disorders in immunocompetent and immunocompromised patients.^{12–14} In addition, an age-related restriction of T-cell receptor repertoire cannot be excluded. We propose that, in this case, the T-cell oligoclonal population may have been selected during the development of EBV+ DLBCL, but expanded only after the elimination of the EBV+ B-cell clone by R-CHOP therapy. This scenario would establish immunodeficiency as a unifying pathogenic link leading first to the EBV-driven proliferations and then to an exaggerated oligoclonal T-cell expansion amounting to a malignant lymphoma. We consider it a possibility of utmost clinical relevance that anti-CD20 therapy might act as a second hit in an already immune defective niche allowing the T-cell oligoclone to expand.

Currently, there are no data on subclinical age-related immunodeficiencies and their histological manifestations. Diagnostic biopsies performed for CVID in adults are rarely encountered in routine pathological practice with only 17 patients identified between 1959 and 1991 in a National Cancer Institute (NCI), Bethesda study.¹⁵ The histological presentation of lymphoid hyperplasia is non-specific and this case highlights the importance of clinicopathological collaboration. EBV+ cells associated with granulomatous reaction should have raised suspicions of impaired immunity. Furthermore, this case provides a strong argument for biopsy and the use of adequate immunohistological investigations in cases of recurrent lymphadenopathy in lymphoma patients.

In summary, we present a case of a duplex malignant lymphoma with T-cell after B-cell sequence, a rare occurrence in non-transplanted patients. We have hypothesised that immunodeficiency may have factored in their pathogenesis. We also propose that iatrogenic factors may have contributed to further dysregulation of the adaptive immune system allowing T-cell expansion.

Competing interests None.

Patient consent Obtained.

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Learning points

- This case highlights the need for awareness of the varied clinical presentations of, and the criteria for, common variable immunodeficiency, particularly in cases with recurrent lymphadenopathy.
- The importance of vigilance in the follow-up of lymphoma patients.
- The importance of considering iatrogenic causes in secondary malignancies.
- This case also emphasises the necessity for rebiopsy and the use of adequate immunohistological investigations in patients with a history of previous lymphoma and recurrent lymphadenopathy.

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