CASE REPORT

PAX5-expressing ALK-negative anaplastic large cell lymphoma with extensive extranodal and nodal involvement

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SUMMARY

A 55-year-old man with a history of well controlled HIV infection was admitted with acute renal impairment, peripheral oedema, constitutional symptoms, deranged liver function and hypercalcaemia. Core biopsies of a retroperitoneal mass demonstrated anaplastic lymphoma kinase (ALK) negative anaplastic large cell lymphoma (ALCL) with unusual Paired box 5 (PAX5) positivity. The same malignant cells were identifiable on urine cytology. Staging investigations revealed extensive nodal and extranodal disease including ALK negative ALCL involving the kidney and prostate, which has not previously been reported in the published literature.

proteins. In contrast to ALK⁺ ALCL, peak incidence of ALK⁻ ALCL is in adults (median age at diagnosis 40–60 years) rather than in children or young adults, and extranodal disease is less common. Most patients present with stage III–IV disease and B symptoms. Its aggressive course leads to a poorer prognosis than ALK⁺ ALCL (3-year overall survival 62% vs 89%, 5-year overall survival 37–58% vs 70–93%).^{3–6}

We discuss an interesting case of ALK⁻ ALCL with extensive extranodal disease including uncommon sites of involvement, unusual weak PAX5 positivity on immunohistochemistry and positive urine cytology, on a background of well-controlled HIV infection.

BACKGROUND

Anaplastic large cell lymphoma (ALCL) is an uncommon CD30⁺ peripheral T-cell neoplasm that represents 2–3% of non-Hodgkin lymphoma (NHL) and 12% of T-cell NHL.¹ Anaplastic lymphoma kinase (ALK)⁻ ALCL is a provisional entity in the WHO 2008 Classification² and constitutes 15–50% of all ALCL cases.¹ Unlike ALK⁺ ALCL, ALK⁻ ALCL does not express the ALK protein. It is otherwise morphologically indistinguishable from ALK⁺ ALCL. The majority of cases demonstrate expression of T-cell associated markers and cytotoxic granule-associated

CASE PRESENTATION

A 55-year-old man was admitted with acute renal impairment following 3 months of flank pain, drenching sweats, unintentional weight loss and gross peripheral oedema. He had a history of HIV infection treated with a combination of emtricitabine, tenofovir and raltegravir as antiretroviral therapy (diagnosed in 1995; CD4 count >500 per/uL and undetectable viral load within the preceding 12 months) and recent removal of a ureteric stent for a right ureteric stricture (no malignant cells on biopsy or washings from ureteroscopy 2 months prior). He

Figure 1 Retroperitoneal mass with (A) H&E stain showing sheets of large atypical lymphocytes with positive staining for (B) CD30 and (C) Pax5 (weak).

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Figure 2 Retroperitoneal mass biopsy with H&E stain showing atypical lymphoid cells infiltrating skeletal muscle.

Figure 4 Peripheral blood smear showing a circulating lymphoma cell.

had an Eastern Cooperative Oncology Group (ECOG) performance status⁷ of 3.

Abdominal CT revealed bulky retroperitoneal lymphadenopathy forming a 29×5×5 cm conglomerate mass encasing multiple structures including both ureters. Subsequent neck and chest CT displayed mediastinal and left supraclavicular lymphadenopathy, a moderate right pleural effusion, left lower lobe pulmonary nodules and bladder base thickening. Full blood examination showed haemoglobin of 104 g/L, total white cell count of 17×10^9 /L and platelet count of 843×10^9 . The patient developed hypercalcaemia (corrected calcium 3.50 mmol/L) and worsening liver function in a mixed hepatitic and cholestatic pattern (alanine aminotransferase 102 U/L, γ -glutamyl transferase 2226 U/L, alkaline phosphatase 1750 U/L and normal bilirubin levels). Lactate dehydrogenase on admission was elevated at 384 U/L (normal range 125–255 U/L).

Bilateral ureteric stents were inserted, complicated by aspiration pneumonitis. The hypercalcaemia responded to intravenous bisphosphonates and hydration. Subsequent CT-guided biopsy of the retroperitoneal mass demonstrated histology consistent with ALK⁻ ALCL (figures 1 and 2). The large atypical lymphoid cells showed positive immunoperoxidase staining for CD30, epithelial membrane antigen (EMA), CD4, T-cell intracellular antigen (TIA)-1, granzyme B (patchy) and PAX5 (weak diffuse). Other than weak Pax5 positivity, there was no staining

for other B-cell markers (CD20 and CD79a), T-cell markers (CD2, CD3, CD5), ALK1 and CD15. Although there was PAX5 positivity, classical Hodgkin lymphoma was considered unlikely given the morphology and lack of CD15 expression. Prior to the biopsy, urine cytology had found morphologically identical cells that were thought to be attributable to a high-grade urothelial carcinoma (figure 3). These cells were subsequently found to stain positively for CD30, Pax5 (weak) and leucocyte common antigen (LCA), indicative of urinary tract involvement by ALCL. Peripheral blood smear also revealed occasional atypical lymphocytes suspicious for circulating ALCL (figure 4).

Bone marrow biopsy showed involvement with similar large atypical cells that were CD30 positive, and negative for CD20, CD3, ALK and PAX5 (figure 5). Positron emission tomography (PET) scanning revealed multiple nodes above and below the diaphragm, and widespread extranodal disease involving the peritoneum, liver, stomach, bowel, muscle, lung, kidney, prostate, bladder and bone (figure 6). MRI of the brain showed multiple intraosseous lesions but no intra-axial lesions. The first cerebrospinal fluid (CSF) collection was unremarkable, however, a second lumbar puncture revealed the neoplastic cells on cytology. There was the presence of a small T-cell receptor gene rearrangement in a peripheral blood sample. Immunoglobulin heavy chain gene rearrangement was not performed due to issues with DNA amplification on the peripheral blood sample.

Figure 3 (A) Urine cytology Pap stain highlighting three large malignant cells and (B) cell block preparation containing CD30⁺ cells.

Figure 5 Bone marrow trephine with CD30 stain revealing a cluster of CD30 positive cells.

Figure 6 Positron emission tomography (PET) scan showing extensive fluorodeoxyglucose (FDG) avid disease.

TREATMENT AND FOLLOW-UP

A first cycle of chemotherapy with cyclophosphamide, doxorubicin, etoposide, vincristine and prednisolone was started on day 19 of admission. At present, 6 months after initial diagnosis, the patient has completed four cycles of chemotherapy. Complications have included prolonged cytopenias resulting in omission of etoposide from cycle 2, and a decline in left ventricular ejection fraction leading to substitution of doxorubicin with epirubicin from cycle 3. A recent PET scan confirmed complete metabolic remission and CSF cytology was negative for malignancy. Autologous stem cell transplantation is currently being considered.

DISCUSSION

Our patient presented with extensive extranodal (peritoneum, liver, stomach, bowel, muscle, lung, kidney, prostate, bladder, bone, bone marrow, CSF) disease. This is unusual because presentation with extranodal involvement appears to be more common in ALK⁺ ALCL rather than ALK⁻ ALCL.^{1 2 8} To our knowledge, this is the first reported case of ALK⁻ ALCL involving the kidney and prostate. This case also adds to the few reports of ALK⁻ ALCL involving the liver,^{5 9} lung,^{5 9} bone,^{5 9} bone marrow^{5 9 10} and skeletal muscle.¹¹⁻¹³ There are single case reports of ALCL involving the peritoneum (ALK status unknown),¹⁴ kidney (ALK⁺),¹⁵ bladder (ALK⁺ and ALK⁻)¹⁶⁻¹⁹ and prostate (ALK⁺).¹⁶ In contrast to our patient, one study observed that there was a greater proportion of patients with bone and bone marrow involvement in their ALK⁺ compared to their ALK⁻ group.⁵ It may be that the biology of ALCL in patients with HIV differs from that in the non-HIV population.

A review paper of 36 published cases of HIV-associated ALCL demonstrated that all the examined cases had extranodal disease, while only 10 had nodal disease, but in half of these cases the ALK status was not stated, making direct comparison difficult.²⁰

Urine cytology revealing ALCL has been described in three cases involving ALK⁺ ALCL. In two cases, lymphoma had invaded into the bladder wall.^{17 21} In the other, it was unclear if there was urinary tract involvement allowing the shedding of tumour into the urine.²² Because of the small numbers of reports, the yield of performing urine cytology in the context of ALCL remains unknown. However, urine cytology has been a diagnostic tool in other lymphomas with urinary tract disease, including diffuse large B-cell lymphoma,²³⁻²⁵ Burkitt lymphoma,²⁶ extracavitary primary effusion lymphoma²⁷ and Hodgkin lymphoma.²⁸ Hence, in the patient with suspected lymphoma in the urinary tract, it may be a helpful adjunct to diagnosis.

A study by the Concerted Action on SeroConversion to AIDS and Death in Europe (CASCADE) collaboration suggested that within the HIV population, those who underwent seroconversion at an age greater than 25 years or had HIV infection through male homosexual exposure were a high risk group for the development of NHL.²⁹ In this high risk group, they estimated that in the highly active antiretroviral therapy era, the estimated incidence of NHL at CD4 counts of above 350/mm³ is 1.4/1000 person-years (95% CI 0.7 to 2.7),²⁹ compared to an incidence of under 0.2/1000 person-years in the general population.³⁰ However, there appears to be little gradient in NHL incidence by CD4 cell count categories until CD4 counts below 100/mm³, when the incidence dramatically rises.²⁹ Of interest, our patient's CD4 counts had been 400–700/mm³ between

October 2006 and July 2013, with the latest CD4 count being 551/mm³ in July 2013. His CD4 count on presentation with the presence of NHL, in the setting of being unwell, was 287/mm³. This highlights the need to maintain a high index of suspicion for lymphoma in HIV-infected patients, irrespective of a reasonably preserved CD4 count. Data from the UK Collaborative HIV cohort supports this contention; they demonstrated that although the risk of developing NHL continues to be directly related to most recent CD4 counts, a significant 50% of HIV patients presenting with systemic NHLs had a median CD4 count >200/mm³ (25% had median CD4 counts of >350/mm³).³¹

The diagnosis of ALK[−] ALCL involves distinguishing it from CD30⁺ neoplasms including ALK⁺ ALCL, primary cutaneous ALCL, classical Hodgkin lymphoma and other subtypes of CD30⁺ T-cell or B-cell lymphoma with anaplastic features. PAX5 is a transcription factor that is necessary for B lineage commitment,^{32–33} is consistently expressed in B-cells from the pro-B to mature B-cell stage and is used as a marker for B-lineage by immunohistochemistry among the lymphomas.^{34–35} It is helpful in distinguishing ALCL from classical Hodgkin lymphoma, typically demonstrating weak staining in the latter and staining negative in the former.² There are only a few other cases in the published literature of PAX5 positivity in otherwise characteristic ALCL (eight ALK[−], one ALK⁺).^{36–38} In five of these cases, it was noted that the intensity of PAX5 staining was similar to that of classical Hodgkin lymphoma. The mechanism for PAX5 positivity is unclear, however, one group identified extra copies of the PAX5 gene locus by fluorescent in-situ hybridisation in all four of their PAX5⁺ ALCL cases, suggesting a possible association between extra copies of PAX5 and PAX5 protein expression in ALCL.³⁶ Molecular analysis has not been routinely used in clinical practice due to the lack of well-established markers to clarify ambiguous cases. Recently, Doring *et al*³⁹ explored gene expression data of microdissected tumour cells of both lymphomas, and found four genes strongly expressed in Reed-Sternberg cells (MDC/CCL22, CD83, STAT3, TUBB2B) that could distinguish Hodgkin from ALK[−] ALCL with reasonable accuracy in a test cohort of 44 patients.

Learning points

- ▶ Suspicion of lymphoma should be high in an HIV-infected patient, irrespective of a preserved recent CD4 count.
- ▶ PAX5 immunohistochemistry is often a useful marker for B-cell lineage and for distinguishing anaplastic large cell lymphoma (ALCL) from Hodgkin lymphoma. This case, however, is an example of the importance of recognising Paired box 5 (PAX5)⁺ ALCL and avoiding the designation of these neoplasms as B-cell malignancies, which will impact treatment choices and outcomes. PAX5 immunohistochemistry should be interpreted in conjunction with clinical findings, morphological features and assessment of other B-cell and T-cell markers. The role of molecular studies in equivocal cases requires exploration in larger studies.
- ▶ Anaplastic lymphoma kinase (ALK)[−] ALCL can present with extensive extranodal as well as nodal disease.
- ▶ Urine cytology and immunophenotyping may be a non-invasive adjunct to diagnosis in a patient with suspected urinary tract involvement with ALCL.
- ▶ This is the first reported case of ALK[−] ALCL involving the kidney and the prostate.

Contributors DMO collected the relevant clinical information and investigation results, drafted the report, liaised with the patient and obtained patient consent for the publication of information, including images. KDC identified and obtained images for the peripheral blood film, bone marrow pathology and nuclear medicine imaging that are in the report, and reviewed and revised the draft report. AP interpreted the diagnostic biopsy including the histology and immunohistochemistry, obtained images for the histology and cytology that are in the report, and reviewed and revised the draft report, particularly from an anatomical pathology perspective. GG initiated the case report as the initial treating haematologist, and reviewed and revised the draft report, particularly from a haematology perspective. All the authors provided final approval of the version to be published.

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