**Case Report**

**Cytokine nephropathy and multi-organ dysfunction in lymphoma**

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**Introduction**

We report two cases of renal, hepatic and respiratory failure occurring with the haemophagocytic syndrome (HPS) in association with occult peripheral T-cell lymphomas. The haemophagocytic syndrome has recently been recognised to occur in association with massive cytokine release, however there have been no documented reports of hypercytokinaemia occurring together with acute renal or hepatic failure. In both these cases the renal failure was secondary to an acute tubular necrosis-like lesion, together with severe interstitial oedema, but in the absence of either glomerular pathology or cellular infiltration. In addition there was no lymphomatous infiltration of the liver to explain the hepatic failure. These findings occurred in the setting of very high cytokine levels and in the absence of any obvious ischaemic or toxic insults.

We suggest that the hypercytokinaemia may be a direct cause of the renal, hepatic and pulmonary failure, and present the two cases together with evidence supporting this hypothesis.

**Case 1**

A 59-year-old Caucasian man initially visited his general practitioner with a 2-week history of fevers, anorexia and weight loss. He was prescribed amoxycillin but over the subsequent week became jaundiced and was referred to hospital. At this stage he had a normal blood count but abnormal liver enzymes (ALT 333 U/l, ALP 213 U/l) and mildly impaired renal function (urea 10 mmol/l, creatinine 115 mmol/l). Both renal and hepatic function deteriorated over the following 2 days and he was transferred to the liver unit at this hospital.

On examination he was febrile (39°C). Cardiovascular, respiratory, and neurological systems were all normal. There was no lymphadenopathy; however, his liver extended 4 cm below the right costal margin and the spleen was just palpable. Urine output was 20 ml/h with only red cells detected in his urine. 

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and confirmed by another supraregional lymphoma laboratory. Cytokine levels were measured retrospectively on stored serum by ELISA and expressed as the mean and standard error. Serum TNFα levels were found to be highly raised $91 \pm 24\, \text{pg/ml}$ (normal $6 \pm 2\, \text{pg/ml}$), with IFNγ being $15 \pm 7\, \text{IU/ml}$ ($0.2 \pm 0.1\, \text{IU/ml}$). IL-6 was only marginally in raised and IL-2 was virtually undetectable ($n = 7$ samples).

**Case 2**

A 46-year-old Ghanaian male, who had been resident in the UK for 15 years, presented with a 1 week history of fevers, myalgia, headache and anorexia. Despite broad-spectrum antibiotics his condition did not improve, and in view of deteriorating renal function he was referred to the renal unit at this hospital. On examination he was febrile ($40^\circ\text{C}$), tachycardic, but otherwise cardiovascularly stable. He had no peripheral lymphadenopathy, but was tender in the right upper quadrant and had a 6-cm palpable hepatomegaly but no palpable spleen. His urine output was approximately 30 ml/h, phase-contrast microscopy showed haematuria but inactive sediment. Full blood count was normal apart from a haemoglobin of 10.2 g/dl. He had normal electrolytes but a urea of 24.6 mmol/l and creatinine of 589 mmol/l. His liver function tests were also abnormal (bilirubin 12 μmol/l, AST 86 U/l, ALT 68 U/l, ALP 59 U/l, albumin 20 g/l, INR 1.2). Other abnormal results included triglycerides, which were elevated at 14.85 mmol/l, ferritin was 4350 μg/l and LDH 1657 U/l.

Serology for EBV was positive for IgG but negative for IgM. Serological analysis and culture revealed no other evidence of current or recent infection. All autoantibodies were negative. Ultrasound revealed normal sized, hyperechoic but unobstructed kidneys, confirmed the hepatomegaly and revealed mild ascites.

A renal biopsy showed acute tubular necrosis with marked interstitial oedema and a minimal chronic interstitial inflammatory infiltrate. Again there was no evidence of either glomerular pathology or a vasculitis. A liver biopsy demonstrated histiocyte (CD68 and S100 positive) infiltration of sinusoids. The portal tracts were infiltrated with cells including lymphoid blasts of mixed T-cell (CD3) and B cell (CD 20) and marked haemophagocytosis was seen. With progressive deterioration of renal and hepatic function the patient required intermittent haemodialysis. He developed a pancytopenia and respiratory distress. In the absence of a firm diagnosis he underwent a bone-marrow aspirate and an open-lung biopsy. The former showed marked haemophagocytosis and a reduction in all cell lines. Lung biopsy showed histiocyte infiltration (CD68, S100) with markers of intense activation (CD4, RFD7 and RFD 1μ) but no evidence of granulomata. Lymphoid blasts were also present but T-cells (CD3) and B-cells were sparse (CD20) with a CD4:CD8 ratio of 1.4. Empirical treatment with intravenous immunoglobulin and steroids was tried, and there was a cholestasis together with foamy Kupffer cells and histiocytes in the sinusoids.

Despite supportive treatment, including haemodialysis, the patient’s hepatic function continued to deteriorate he developed respiratory distress and died of multi-organ failure approximately 6 weeks after the start of his illness. A post-mortem examination revealed massive hepatic necrosis. The peripancreatic lymph nodes were only mildly enlarged, but histological examination showed abnormal architecture with large serpiginous zones of necrosis, haemophagocytic histiocytes (Figure 2), and large multinucleate blasts. In addition there was a pleomorphic population of intermediate-sized blast cells expressing CD3 (T-cell marker) and CD45RO (activation ‘memory’ T-cell marker) but lacking either CD4 or CD8. The larger of these cells expressed CD30 (activation marker). No evidence of late EBV antigens was found in the sections by immunostaining. As the diagnosis was made at post-mortem no fresh tissue was available for T cell receptor rearrangement or EBV PCR studies. The appearances were classified as a pleomorphic large T-cell lymphoma in the Kiel and REAL classifications.
transient symptomatic improvement. Despite continued renal support his condition continued to deteriorate such that he was unable to receive further chemotherapy and he died from multi-organ failure. At post-mortem enlarged cervical and para-aortic nodes were noted, the largest being 1.5 cm in diameter. The architecture of the para-aortic nodes had been completely effaced, on high power there was widespread replacement of normal cells by large and bizarre forms (Figure 3a). These cells were positive for the T cell marker CD3 (Figure 3b), indicating a peripheral T-cell lymphoma. Post-mortem EBV DNA was detected in serum samples by PCR. TNFα and IFNγ were raised 118 ± 37 pg/ml and 5.1 ± 2.8 IU/ml respectively (normal 6 ± 2 pg/ml, 0.2 ± 0.1 IU/ml), while IL-6 was noted to be 137 ± 31 pg/ml (normal 3 ± 2 pg/ml). IL-2 levels were within the normal range (n = 5).

Discussion

We have described two patients with occult peripheral T-cell lymphoma presenting with severe renal and hepatic failure. The most common renal complication of lymphoma is a minimal-change glomerular lesion but numerous other presentations are well described including membranoproliferative and membranous glomerulonephritis, infiltration and obstruction [1–3]. All of these were excluded in our patients. Hepatic failure in lymphoma is usually due to direct infiltration of liver parenchyma, although a cholestatic picture may occur as a non-metastatic manifestation. We felt unable to diagnose the hepatorenal syndrome in our two patients due to the findings at renal biopsy and the urinary electrolytes [4].

In both cases haemophagocytosis was a major feature, and this phenomenon describes macrophage engulfment and destruction of cells usually of the haemopoetic lineage. Haemophagocytosis may be a consequence of any intense macrophage activation and is seen in histiocytic and non-histiocytic disorders. The Histiocyte Society classified the haemophagocytic syndromes into three groups [5]. The first is Langerhan cell histiocytosis, which is often seen in children but presenting less diagnostic difficulty than the other groups, and which may require cytotoxic chemotherapy. The second is histiocytosis of mononuclear phagocytes other than Langerhan cells; this group is further divided into haemophagocytic lymphohistiocytosis (HPH) which may be familial and fatal, and the infection associated haemophagocytic syndromes. Lastly are the true malignancies of histiocytes. In this paper we concentrate on secondary activation of macrophages and the group of infection-related haemophagocytic syndromes, a category that has expanded to encompass those associated with malignancies, particularly lymphoma [6]. In one study, half of the cases were due to haematological malignancies, in particular peripheral T-cell lymphomas [7]. Numerous viral infections, especially Epstein–Barr virus and other herpes viruses, are also important associations [8]. In one review of HPS, 11 of 25 patients had uraemia but the cause of the renal impairment was not specified and hepatic dysfunction was not documented [6].

A number of cytokines are upregulated in HPS, including interferon gamma (IFNγ), tumour necrosis factor alpha (TNFα), interleukin 6 (IL-6), soluble interleukin 2 receptor (sIL-2R), soluble CD8 and macrophage colony-stimulating factor [9]. These elevated plasma cytokine levels have been implicated in the hyperactivation of macrophages that leads to engulfment and destruction of an expanded range of targets. Circulating levels of both IFNα and sIL-2R have been shown to correlate inversely with survival in the haemophagocytic syndrome [10].

With advances in the field of cytokine biology, and in particular novel therapies in organ transplantation and oncology, our understanding of the effects of elevated cytokine levels has expanded. Therapeutic use of IFNγ frequently causes fever, myalgia and lethargy, and renal side-effects are described including acute tubular necrosis [11], interstitial oedema, and glomerulopathy [12], and at high doses severe hepatic dysfunction can occur [13]. Attempts to use TNFα thera-
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peutically have been disappointing due to toxicity problems. TNF causes a 'flu-like syndrome with hypotension and hepatotoxicity [14]. Animal studies looking at infusion of TNF have reported both acute tubular necrosis and pulmonary dysfunction due to ATN with severe interstitial oedema. TNF has been implicated in the pathogenesis of the renal disease, particularly since the viruses themselves are not cytolytic [16]. Recently a study of EBV positive and negative lymphomas demonstrated that TNF was expressed in 57 and 40% of EBV-positive T cell and B cell lymphomas respectively while it was only expressed in 17% of EBV-negative ones. In addition the supernatant from cultured T cell lymphoma lines enhance phagocytosis and secretion of TNF and IFN. This could be inhibited by either anti-TNF or anti-IFN antibodies [16]. Elevated TNF also explains the high triglyceride levels as it inhibits lipoprotein lipase activity in adipocytes and stimulates hepatic lipogenesis [17].

Fas (Apo1, CD95) is a membrane protein related to the TNF receptor family, and is expressed in a number of tissues including liver, lung and renal tubular cells. When bound to its ligand (fasL) it is able to cause cellular apoptosis. Recent evidence suggests that this cellular signalling pathway has an important role in the progression of viral hepatitis and fulminant hepatic failure. FasL is also released by activated lymphocytes and may be an important pathway of contact independent T cell cytokotoxic activity [19], and this is further substantiated by the ability of a neutralizing antibody to fasL to prevent T cell induced hepatic injury caused by concanavalin A [20]. Both Fas and fasL are upregulated by TNF and there is evidence that apoptosis may be important in some cases of tubular necrosis [21]. However, in combination, TNF and IFN alone can induce hepatocyte apoptosis [22]. Additionally TNF can cause changes in cell surface localization of receptors such as adhesion molecules, which may be important for cell–cell communication, or the recruitment of inflammatory cells [23].

The murine monoclonal antibody OKT3 used in organ transplantation is frequently complicated by a 'flu-like illness, reversible renal dysfunction [24], and pulmonary capillary leakage [25]. It is thought that these effects are consequent upon profound T-cell activation and release of TNF, IFN and IL-2 [26], hence the term 'cytokine nephropathy'. These side-effects can in part be ameliorated by corticosteroids, which suppress this cytokine production.

The outcome in adult patients with HPS is poor unless chemotherapy is started early and even then it has a mortality of approximately 60% [27]. Often it is impossible to prove the diagnosis of an underlying lymphoma and there is frequently little or no peripheral lymphadenopathy. Premature treatment with cytotoxic agents could result in chemotherapy being administered to patients with viral infections, in whom spontaneous recovery from HPS may otherwise approach 70% [28].

Despite this reservation some authors advocate cytotoxic treatment on clinical grounds without waiting for viral titres or positive lymphoma histology [27]. Theoretically anti-TNF antibody may be very useful in this condition.

We propose that cytokine overproduction is central to the organ dysfunction, but what is not clear is the origin of these cytokines, since many of them may be produced the tumour cells, or by active macrophages themselves, causing a self-perpetuating vicious circle. Given that lymphomata have been found in these two patients, and there was no other pathology discovered, it is likely that cytokine release from the tumours is at least an initiating, and possibly a perpetuating factor in the macrophage activation. It is interesting to note that EBV DNA was detected in the second patient and it seems most likely that the lymphoma was EBV related. The role of fas/fasL in this condition is not clear but fasL is a cytokine that might be expected to be upregulated in T-cell lymphoma and would be well worth measuring.

We have presented two cases of occult T-cell lymphoma with the unusual and ominous feature of haemophagocytosis. This syndrome has been linked to elevated cytokine production. The presentation of hepatic and pulmonary failure together with features of acute tubular necrosis and marked interstitial oedema, in the absence of obvious toxic, ischaemic, or infective causes, led us to measure cytokine levels. We believe that the systemic, renal, hepatic, pulmonary and macrophage abnormalities in these may well be due in part to the excessive release of cytokines, particularly TNF and IFN (Figure 4), by lymphomatous T cells.

References
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