CASE REPORT

Severe acute kidney injury as presentation of Burkitt's lymphoma

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SUMMARY

We discuss a case of acute kidney injury (AKI) at a very young age caused by primary lymphomatous renal infiltration due to Burkitt's lymphoma and analyse the literature on this rare condition. At presentation, clinical examination showed impressive bilateral nephromegaly and hypertension. Blood analysis indicated severe AKI, mild anaemia and normal serum electrolytes. There were no signs of tumour lysis syndrome. Urine sediment was normal, with neither haematuria nor proteinuria. Abdominal ultrasound demonstrated bilateral renal enlargement (+12 SD), with increased corticomedullary differentiation. MRI demonstrated the presence of a homogenous renal enlargement with features of an infiltrative lesion. Ultimately, microscopic and immunohistochemical analysis of the renal biopsy confirmed the diagnosis of Burkitt's lymphoma. Early and aggressive therapy is the key to ensure a good outcome.

BACKGROUND

Acute kidney injury (AKI) is a life-threatening condition that accounts for 2–3% of admissions in paediatric tertiary centres. In the last two decades, incidence is increasing mainly because of the nephrotoxic side effects of new drugs.^{1 2}

In patients with cancer, AKI is even more common, either secondary to the side effects of chemotherapy or as a direct consequence of malignancy: (1) Volume depletion related to anaemia, vomiting or diarrhoea can cause prerenal AKI. (2) Obstruction of the urinary tract due to tumour mass is an important postrenal cause. (3) Tumour lysis syndrome (TLS), an intrinsic cause of AKI, is an oncological emergency resulting in hyperuricaemia, hyperkalaemia, hyperphosphatemia and hypocalcaemia, with a risk of cardiac arrhythmias, seizures and death due to multiorgan failure. (4) Renal tumours or malignancies with renal involvement may cause or aggravate AKI.^{3 4} Recently, it has been described that despite the fact that renal tumours in children occur in only 6.64 patients per million per year (nephroblastoma 90%, renal cell carcinoma 9%), its incidence is increasing.⁵ Furthermore, a particular link between cancer and AKI exists in lymphomas. In advanced stage disease, secondary infiltration of the kidneys is common, but seldom presents with AKI, and renal invasion is often diagnosed postmortem.⁶ In addition, only a few cases of primary renal lymphomas (PRLs) seeming to originate from the kidneys have been described, however, this is extremely rare in children.^{7–13} PRL is less disseminated, but always

presents with AKI. Prompt diagnosis is crucial to initiate chemotherapy, to prevent irreversible loss of kidney function.

In this paper, we describe the unusual presentation of a young Caucasian boy with AKI and nephromegaly caused by PRL, and give an overview of the literature.

CASE PRESENTATION

A 4-year-old boy presented with a 14-day history of general weakness, anorexia, vomiting and abdominal pain. There was history of neither diarrhoea nor fever. Personal and family history were unremarkable.

Physical examination revealed mild dehydration, tachypnoea and malignant arterial hypertension (176/119 mm Hg; +2 SD for sex, age and height was 118/76 mm Hg). The abdomen was bloated with two non-tender masses in the upper quadrants on palpation. No peripheral lymphadenopathies were found.

INVESTIGATIONS

Biochemical examination revealed haemoglobin of 8.5 g/dL (11.5–13.5 g/dL), white cell count of 9200/mm³ (5500–15 500/mm³) and platelet count of 224 000/mm³ (150 000–450 000/mm³). C reactive protein was normal. Plasma sodium was 141.9 mmol/L (135–145 mmol/L) and potassium was 4.19 mmol/L (3.5–5.1 mmol/L). Plasma urea and creatinine were 97 mg/dL (<48 mg/dL) and 2.9 mg/dL (0.26–0.42 mg/dL), respectively. Estimated glomerular filtration rate was 33 mL/min/1.73 m². Lactate dehydrogenase was 5860 U/L (135–250 U/L). Uric acid was 8.9 mg/dL (2–5.5 mg/dL), phosphorus level was 1.62 mmol/L (1.45–2.10 mmol/L) and calcium was 2.4 mmol/L (2.2–2.64 mmol/L). Urinalysis showed neither leukocyturia, haematuria nor proteinuria. Urine output was 0.9 mL/kg/h.

Ultrasonography (US) demonstrated hepatosplenomegaly (+3.2 SD), and bilateral renal enlargement (right 14 cm (+12 SD) and left 13.5 cm (+11 SD)), with increased corticomedullary differentiation, without hydronephrosis. MRI confirmed homogenous renal enlargement, with features of an infiltrative lesion (figure 1A). The pancreas and the spine were both invaded, but cerebrospinal fluid was negative for malignant cells. Neither the US nor MRI showed lymph node enlargement.

Since microscopic analysis of bone marrow aspirate was negative, a renal biopsy was performed. This revealed infiltration by Burkitt's lymphoma: diffuse, medium-sized lymphoid infiltrate, with little basophilic cytoplasm, and large combined

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Figure 1 (A) Coronal T2-weighted MRI of the abdomen showing bilateral homogenous, enlarged kidneys. (B) Neoplastic alteration of the kidney by Burkitt's lymphoma cells, overgrowing the residual glomeruli (g) and tubuli. Immunohistochemistry staining showing uniform nuclear expression of CMYC in the neoplastic cells, as a consequence of the hallmark translocation t(8;14)(q24;q32), causing dysregulation of the MYC gene, which plays a role in cell cycle progression, apoptosis and cellular transformation (anti-CMYC, $\times 200$).

with small distinct nucleoli could be seen on H&E stains. Interspersed apoptotic bodies and tangible-body macrophages were present, creating the characteristic starry-sky appearance of Burkitt's lymphoma. The neoplastic cells expressed CD20, CD10 and CMYC, but no Bcl2 (figure 1B). Fluorescence in situ hybridisation analysis showed at (8;14)(q24;q32). Epstein-Barr virus was not found.

TREATMENT

Chemotherapy according to the Inter-B-NHL rituxan 2010 protocol was initiated. This protocol is a malignant B-cell lymphoma chemotherapy based regimen including cyclophosphamide, vincristine, prednisone, adriamycin, methotrexate, cytarabine and etoposide. During the first week of chemotherapy, haemodialysis was required due to TLS.

OUTCOME AND FOLLOW-UP

At last follow-up, 26 months after diagnosis, blood pressure and renal US were normal with a glomerular filtration rate (GFR) of 61 mL/min/1.73 m².

DISCUSSION

We present a case of AKI caused by primary lymphomatous infiltration of the kidney by Burkitt's lymphoma. Non-Hodgkin lymphoma (NHL) is one of the commonest subtypes of malignancy in children (7%). It develops in lymphocytes and multiple subtypes have been described. Burkitt's lymphoma, named after Denis Parsons Burkitt, is the most prevalent subtype and accounts for approximately 45% of paediatric cases. It is a poorly differentiated lymphocytic lymphoma, consisting of monoclonal proliferating B-lymphocytes, with a characteristic underlying MYC translocation at 8q24. This translocation is characteristically with a partner immunoglobulin gene that is most often IgH at chromosome 14q32. Occasionally, other translocations may be present. This tumour predominantly affects children aged from 5 to 14 years, and is probably the fastest growing tumour in humans. As a consequence, more than 70% of patients present with advanced disease at diagnosis. Thanks to the use of intensive multiagent chemotherapy, most patients with Burkitt's lymphoma can now be cured, with 5-year event-free survival above 80%.^{14 15}

Secondary lymphomatous infiltration of the kidneys is common in NHL. However, AKI as the initial symptom is rare. On the contrary, PRL as described in our case is almost invariably associated with AKI at presentation. Only a few case reports in children have been published.^{7–13} The rarity of PRL

in children makes it difficult to diagnose. PRL was first described by Malbrain *et al*,¹⁶ who suggested some criteria to fulfil the diagnosis: (1) AKI is required at initial presentation; (2) renal enlargement is present with neither obstruction nor extrarenal lymphomatous involvement; (3) diagnosis is made by renal biopsy; (4) other causes of AKI are excluded and (5) chemotherapy provides rapid improvement.

While MRI showed infiltration of the spine and pancreas in our case, we believe this had been caused by secondary infiltration due to the aggressively growing tumour starting in the kidney.

PRL as a clinical entity is still being discussed. Indeed, kidneys do not contain lymphatic tissue, which makes it hard to understand how PRL could develop there. On the contrary, the pathogenesis of secondary lymphomatous infiltration of the kidney is clear: the primary tumour can spread haematogenously or extend directly from the retroperitoneum. On the basis of the sparse evidence that exists today, this puzzle cannot be solved. However, the case described above proves that the kidney could be the primary organ involved. Thus, it is clear that a subtype of NHL that presents with renal invasion and concomitant AKI exists. Disregarding the semantic discussion, the term 'PRL' provides a good description for this specific subtype.

Finally, Törnroth *et al* tried to unravel the mechanism of AKI in PRL. In a cohort of five adult kidney biopsies compared with 50 adult kidney biopsies from the literature, two patterns of lymphomatous infiltration were distinguished: an interstitial and an intraglomerular/intravascular type. In the first, interstitial proliferation of lymphoma cells causes increased intrarenal pressure, subsequently causing AKI. Renal parenchymal elements are pushed aside, explaining the extreme nephromegaly. The second type causes AKI by obstructing the glomeruli. Obviously, this pattern is associated with proteinuria and haematuria, which resembles glomerulonephritis.¹⁷ In the paediatric case we described, AKI was caused by the interstitial type and may explain the absence of haematuria and proteinuria.

Notably, our patient had stage 2 chronic kidney disease (CKD) at follow-up. The current literature is inconclusive as to whether AKI can be a direct cause of CKD. However, it is clear from multiple studies that patients with AKI have a higher risk of developing CKD, especially in patients with cancer. Again, the causality of AKI cannot be confirmed. Close follow-up was advised and performed in our patient.^{18–20}

Although rare, PRL should be considered in children with unexplained AKI and bilateral nephromegaly. Young age does not preclude the diagnosis. When suspected, especially in

enlarged kidneys without an aberration in urinalysis, confirmatory renal biopsies should be obtained and therapy initiated as soon as possible to avoid irreversible renal impairment.

Learning points

- ▶ While renal invasion by lymphoma is common, acute kidney injury (AKI) is seldom part of the presenting symptoms. Primary renal lymphoma (PRL) is very rare, especially in children. This condition does present with AKI.
- ▶ PRL should be considered when children present with unexplained AKI, normal urinalysis and nephromegaly. Our case shows that young age does not preclude the diagnosis.

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