Nephrotic syndrome and Hodgkin lymphoma – an unusual association

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Background
An association between nephrotic syndrome and extrarenal neoplasia was described for the first time in 1922. The reported incidence of nephrotic syndrome in Hodgkin lymphoma is less than 1%.

Clinical description
We present a 13 year old boy who was admitted with complaints of abdominal pain, vomiting and loose stools for 2 months. He had a history of significant weight loss of 5kg in a couple of months.

On examination, he had bilateral pedal oedema and right cervical lymphadenopathy. Cervical lymph node biopsy revealed nodular sclerosis type of Hodgkin lymphoma. He also had hypoalbuminemia, massive proteinuria and hypercholesterolemia.
Secondary nephrotic syndrome due to Hodgkin’s lymphoma was made as a clinical diagnosis.

Management and outcome

He had been started on chemotherapy (with Prednisolone, Vincristine, Doxorubicin, Etoposide) for stage 3B Hodgkin lymphoma. He tolerated the chemotherapy well. Though he had symptomatic edema, managed conservatively as the urine output was adequate. On follow up, he attained spontaneous remission of nephrotic syndrome.

Conclusion

Overt proteinuria might be the manifestation of paraneoplastic syndrome in children with Hodgkin lymphoma and with the management of the primary disease, proteinuria resolves spontaneously.

INTRODUCTION

An association between nephrotic syndrome and extrarenal neoplasia was described for the first time in 1922 [1]. Since then, a large number of cases have been published, few of them describing the link between Hodgkin lymphoma (HL) and nephrotic syndrome.

Though childhood nephrotic syndrome has an annual incidence ranging from 1.2 to 16.9 per 100,000 children, the incidence of nephrotic syndrome in Hodgkin lymphoma is less than 1% [2]. It was observed that nephrotic syndrome and Hodgkin’s lymphoma may present clinically either simultaneously or within several months one after the other. The accurate basis of this relationship rests unknown, even though there have been hypotheses regarding a T-cell dysfunction. The early diagnosis of Hodgkin lymphoma is important as the secondary nephrotic syndrome needs only conservative measures.

Here, we present a 13 year old boy with Hodgkin lymphoma who had nephrotic syndrome as a paraneoplastic manifestation.

CLINICAL DESCRIPTION

A 13-year-old boy was admitted with complaints of abdominal pain, vomiting and loose stools for 2 months. There was a history of swelling of feet and periorbital puffiness noted for 6 weeks; despite which, he had significant weight loss of 5 kg within a couple of months (45 to 40 kg).

There wasn’t any history of fever, bone pain, dyspnea/orthopnea, bleeding manifestations, decreased urine output or altered bowel habits. There was no significant medical illness in the past or contact with tuberculosis. On examination, there was no pallor and icterus. He had firm, non-tender right supraclavicular (4x4 cm) and bilateral lower cervical lymphadenopathy (3x5 cm), periorbital puffiness, ascites and bilateral pitting pedal oedema. His heart rate was 90/min, respiratory rate was 28/min and blood pressure of 100/60 mmHg. Abdomen was distended with no organomegaly and shifting dullness was noted suggestive of ascites. Other system examinations were unremarkable.

Due to the unusual features like weight loss despite edema and cervical lymphadenopathy in an adolescent boy, possibility of an underlying infection (tuberculosis) or malignancy (Hodgkin lymphoma) were considered in the background of nephrotic syndrome.

His complete blood counts, renal functions tests, liver functions tests were normal except hypoalbuminemia, 1.9 g/dL and hypercholesterolemia, 422 mg/dL (10.2mmol/L). Urine routine showed 3+ albuminuria, no hematuria, spot urine protein/creatinine ratio >2 and 24-hour urine protein was 2.4 g. Urine culture was sterile. Antinuclear antibodies, C3 and C4 were normal. Mantoux was not reactive. Chest X-ray was...
normal. ESR was 24 mm. Cervical lymph node excision biopsy revealed loss of lymph node architecture, presence of Reed Sternberg cells, CD15 and CD30 staining which favoured nodular sclerosis type Hodgkin lymphoma (Figure 1). Bone marrow biopsy showed no infiltration by lymphoma. Whole body PET-CT done for staging showed cervical, mediastinal and para-aortic nodes, suggesting stage 3 disease. Secondary Nephrotic syndrome due to Hodgkin's lymphoma was made as a clinical diagnosis.

**MANAGEMENT AND OUTCOME**

He had been started on OEPA based chemotherapy (Prednisolone, Vincristine, Doxorubicin, Etoposide) as per EURONET Protocol for stage 3B Hodgkin lymphoma. He tolerated the chemotherapy well. Though he had symptomatic edema, he had been managed conservatively as the urine output was adequate. On follow up, he attained spontaneous remission of nephrotic syndrome with resolution of clinical edema in 2 weeks and normalisation of serum albumin (3.5 g/dL) along with absence of proteinuria by 5 weeks of chemotherapy (Figure 2).

**DISCUSSION**

Nephrotic syndrome is characterized by heavy proteinuria leading to edema, hypoalbuminemia 3 g/dL and hyperlipidemia (cholesterol > 200 mg/dL or 5.17 mmol/L). Heavy proteinuria is indicated by urine protein of 3+/4+ or spot urine protein/creatinine ratio of >2 or >50 mg/kg/day or > 40 mg/m²/hour in a timed sample [3].

*Figure 1* Results of cervical lymph node excision biopsy

(a) Hematoxylin and eosin stain 40x Large mononuclear RS cell with prominent nucleoli pointed by red arrow. (b) CD45 immunostain 20x Negative in RS cells. (c) EBV LMP immunostain 20x: RS cells were membrane positive. (d) CD15 immunostain 20x: RS cells were positive. (e) CD30 immunostain 20x: RS cells were positive. (f) PAX 5 immunostain 20X: RS cells are weakly positive (pointed by red arrow), reactive B cells are strongly positive.
The kidney can be involved in neoplastic diseases in many ways: direct infiltration, renal vein thrombosis, renal artery or ureter compression by the neoplastic mass, tumour lysis syndrome, chemotherapy induced acute kidney injury, urinary tract infection, thrombotic microangiopathy and paraneoplastic disease. The intimate relationship between kidney and malignancy is bi-directional as oncology patients get various renal manifestations in due course and some nephrology patients who undergo kidney transplant, develop malignancies in the course of their treatment [4]. It is difficult to find the true incidence of glomerular disease caused by malignancy as kidney biopsies are rarely performed in patients with cancer.

Hodgkin and non-Hodgkin lymphomas, and acute myelogenous leukemia are the common malignancies associated with nephrotic syndrome in children [5]. Secondary nephrotic syndrome is thought to be a rare paraneoplastic syndrome of Hodgkin lymphoma (HL). The nodular sclerosis and mixed cellularity type of HL are the predominant histologic subtypes, in both adults and children. The incidence of nephrotic syndrome in Hodgkin lymphoma has been reported in the range of 0.6 to less than 1%. Stephan et al. analysed the prevalence of nephrotic syndrome in patients diagnosed with Hodgkin’s lymphoma and found that 5 out of 483 children suffering from Hodgkin lymphoma, followed for a period of 13 years, developed nephrotic range...
proteinuria [2]. Incidence of 0.6% was reported in a large series from Turkey [6]. In the majority of HL cases associated with nephrotic syndrome, selective albuminuria with normal renal function were the typical manifestation. From India, there were only 2 pediatric cases reported with HL and paraneoplastic syndrome. Both were neurological manifestation, one child with achalasia and Holmes Adie pupil [7] and another child with Ophelia syndrome [8].

Minimal change disease (MCD) is the most common associated pathological lesion with Hodgkin lymphoma. It is postulated that the cause of MCD could be T cell dysfunction with abnormal secretion of cytokines, altering the permeability of the glomerular basement membrane. Other previously reported glomerular diseases include membranous nephropathy, focal segmental glomerulosclerosis, mesangiocapillary glomerulonephritis, anti-glomerular basement membrane nephritis, and IgA nephropathy [9]. Mori reported a 15-year-old boy with frequently relapsing nephrotic syndrome with natural killer (NK) cell deficiency prior to the overt relapse of Hodgkin’s disease. That child attained remission and complete recovery of the NK cell count after the treatment of the HL relapse [10]. Hence, proteinuria can be considered as the possibility of subclinical relapse of the lymphoma on follow up. The timing of nephrotic syndrome presentation in respect of HL varies in literature from months to few years [2].

CONCLUSION

Proper clinical examination is mandatory when facing a child with nephrotic syndrome, in order to exclude malignancies. Overt proteinuria might be the manifestation of paraneoplastic syndrome in children with HL and with the management of the primary disease, proteinuria resolves spontaneously. These children should be followed up as it is being observed that the relapse of the Hodgkin lymphoma causes consecutive relapse of the nephrotic syndrome. It emphasizes the importance of paediatrician, paediatric oncologists and nephrologists working together in managing these children.

LESSONS LEARNT

• Proper clinical examination gives us the lead to primary diagnosis in a child with oedema and proteinuria.
• Paraneoplastic syndrome resolves spontaneously in a child with malignancy when the primary disease is treated.
• Relapse of nephrotic syndrome in a child with Hodgkin lymphoma, might be the manifestation of relapse of malignancy.

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Author contributions

All authors were involved in the diagnosis and management of this case.

Consent

Informed and written consent was obtained from parent.

Ethical approval: Not applicable.

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