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Nephrotic syndrome and Hodgkin disease in children: a report of five cases

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Abstract This report documents the occurrence of a nephrotic syndrome in five children with Hodgkin disease. In two cases the nephrotic syndrome predated the diagnosis of lymphoma by 6 months and 12 months respectively , while in the other three, the two disorders occurred simultaneously. The nephrotic syndrome resolved in four cases during effective treatment for active Hodgkin disease, while proteinuria remained unchanged in the fifth case with partial control of the lymphoma. The occurrence of a nephrotic syndrome as a manifestation of active Hodgkin disease suggests that some immunological abnormalities play a role in the pathogenesis of the association.

Conclusion The possibility of glomerular dysfunction although rare must be considered and actively looked for in all cases of Hodgkin disease. Similarly, any unusual sign or symptom noted in patients with nephrotic syndrome, particularly receiving or having received immunosuppressants, requires thorough investigation to determine the presence or absence of lymphoma.

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Key words Nephrotic syndrome · Hodgkin disease · Children

Abbreviations *CSA* cyclosporine A · *HD* Hodgkin disease · *ITP* immunological thrombopenic purpura · *NS* nephrotic syndrome

Introduction

In two combined series involving about 1700 adults with Hodgkin disease (HD) the frequency of the nephrotic syndrome (NS) was only 0.4% [1]. NS and HD were linked in time in some cases, and NS appears to be a etiologically related to HD. Minimal-change glomerular nephropathy is the most frequently observed renal lesion. However, its incidence in children with HD is not known.

Five out of 483 children with HD seen in France in 40 institutions within the Société française d'Oncologie Pédiatrique over a period of 13 years developed NS and are described below.

Case reports (Table 1)

Case 1

Case 1 (already partially reported [4]), a 10-year-old boy, was admitted because of weight gain, oedema, extreme fatigue and periorbital swelling. His past medical history was unrevealing. The urine was +++ for protein. Laboratory investigations yielded the following values: proteinuria (40 g/l); Na 131 mmol/l; creatinine 89 μmol/l; albuminaemia 22.4 g/l; and triglyceridaemia 2.4 g/l. The nephrotic syndrome was not modified by prednisone (60 mg/day for 4 weeks, and three intravenous boluses of 900 mg methylprednisolone each). Percutaneous renal biopsy showed slight mesangial hypercellularity. No deposits of IgG or complement were found by immunofluorescence. Physical examination showed no liver, spleen or lymph node enlargement. Oral cyclosporine A (CSA) was introduced at 6 mg/kg per day, combined with 60 mg of prednisone daily. Proteinuria fell gradually, and disappeared by cyclosporine treatment day 11. Trough levels of CSA were maintained between 150 and 395 ng/ml. Steroids were tapered to a alternate-day regimen (40 mg every other day) 1 month after

introduction of cyclosporine A, but this was promptly followed by a recurrence of proteinuria. Prednisone, 60 mg/day, was thus maintained for a further month and tapered to 10 mg qod when NS remitted.

Six months after the onset of the renal problem, the patient presented with fatigue, fever, and supraclavicular lymph node enlargement. A chest film disclosed enlargement of the mediastinum. A right supraclavicular lymph node was palpable. A diagnosis of Hodgkin disease, IIBb, "nodular-sclerosis" type, subtype 1, was made.

CSA was withdrawn and the 4-drug VBVP regimen (vinblastin day 1–8, VP-16 days 1–5, bleomycin day 1; prednisone days 1–8) was started on a monthly basis, for a total of four courses. Symptoms and node enlargement remitted after the first course. Massive proteinuria recurred when the child recovered from the aplastic phase induced by the first course of chemotherapy. Prednisone, 60 mg/day for 1 month, failed to induce remission of NS and was discontinued. Pefloxacin was begun (800 mg/day) and the proteinuria disappeared on day 7 of this treatment. Local radiation therapy was delivered to the mediastinum. HD and NS are still in remission 3 years later.

Case 2

Case 2, a 14-year-old girl from Sicily, was admitted for fatigue, night sweats, high spiking fever, anorexia and gross haematuria. She had no history of renal disease. On admission the physical examination revealed pallor, no weight gain, and no pitting oedema; the spleen was enlarged. The chest film showed mediastinal enlargement, which was confirmed by CT. Biopsy of these nodes disclosed HD, of the nodular-sclerosis type, subtype 4S. After the diagnostic work-up she was considered to have stage IIBb HD. Laboratory values were as follows: serum creatinine 70 μmol/l; albuminaemia 15 g/l; proteinuria: 15 g/l; red blood cells in urine 120,000/ml; complement and fraction C3/C4 level in the normal range.

Needle biopsy of the kidney revealed mesangial hypercellularity with moderate IgM+, C1q+ and C3+ deposits. The child received albumin infusions and started the VBVP regimen plus prednisone 40 mg/m^2 per day for a week. Four courses of this regimen led to partial transient regression of the mediastinal mass and disappearance of clinical signs, but proteinuria was unaffected. Early relapse occurred, with tumour progression and an inflammatory syndrome. A course of OPPA (vincristine, days 1, 8 and 15; procarbazine, days 1–15; adriamycin days 1–15; and prednisone 60 mg/m^2 for 2 weeks) was ineffective. Fever and disease activity subsided after two courses of MINE (methyl GAG days 1–5; ifosfamide days 1–5; navelbine days 1–5; VP 16 days 1–3) but her proteinuria remained elevated, at 6 g/24 h, throughout. Treatment was escalated with intensive chemotherapy using a combination of BCNU, aracytine, VP16 and melphalan. She succumbed to veno-occlusive disease of the liver, confirmed histologically on day 12 following reinfusion of autologous bone marrow. Proteinuria was unchanged at the time of death.

Case 3

Case 3, a 12-year-old Moroccan boy, was admitted with ascites, massive oedema and pleural effusion. No lymph node, liver or spleen enlargement was found. Laboratory studies revealed anephrotic syndrome, with proteinuria 4.4 g/day; and albuminaemia 8.5 g/l. Serum complement levels were normal and antinuclear antibodies were absent. Proteinuria resolved on the 13th day of prednisone (2 mg/kg/day), which was gradually withdrawn after 6 months. Biopsy was not performed. He was re-admitted 2 months later for a relapse which resolved after a second course of steroids. One year after the onset of NS, epistaxis and purpura led to the diagnosis of immunological thrombopenic purpura [ITP] (platelet count: 11×10^9/l, antiplatelet antibody positivity and megacaryocytes on the marrow smear). The NS was in remission. Conventional chest X-ray and CT films showed several mediastinal lymph nodes, the largest (diameter 65 mm) situated in the right laterotracheal space. Heterogeneous liver nodules were found on the abdominal scan. IV immunoglobulin infusions did not influence the course of ITP, but three plasmaphereses raised the platelet count to above 120×10^9, allowing mediastinoscopy and biopsy to be performed. Histological examination revealed characteristic mixed-cellularity HD (stage IVBb). The patient was given ten alternating courses of chemotherapy [five MOPP (mechloretamine, vincristine, procarbazine and prednisone), and five ABVD (adriamycin, bleomycin, vinblastin and deticene)], plus mediastinal radiation therapy. The lymphadenopathies disappeared after four courses and ITP remitted. Hodgkin disease is in remission 10 years later, and proteinuria has not recurred.

Case 4

Case 4, a 12-year-old boy, was admitted with the complaints of anorexia, weight loss and fever associated with supraclavicular and mediastinal lymphadenopathies. Stage IIBb mixed cellularity Hodgkin disease was diagnosed, proven by peripheral node biopsy. Laboratory studies showed: proteinuria (3.20 g/day) with hypoalbuminaemia (17 g/l). Serum complement levels were normal; ESR was 145. Renal biopsy was not performed. Proteinuria resolved on the 11th day of the first MOPP regimen. Lymphoma remission was obtained after two courses of MOPP and 2 ABVD, in addition to mediastinal radiotherapy. Fever and mediastinal reenlargement on the chest film occurred 14 months later. A second remission was obtained by chemotherapy (three courses of MINE) followed by intensive chemotherapy, autologous bone marrow transplantation and local irradiation and has been persisting for 3 years. Proteinuria did not recur throughout the period of relapse and subsequent therapy.

Case 5

Case 5, a 15-year-old girl was seen for an explained fever and fatigue. Urinalysis showed a massive proteinuria: 6 g per day and rare erythrocytes in the sediment. Initial laboratory studies included: ESR: 120; serum creatinine: 48 μmol/l; total serum protein: 58 g/l; albuminaemia: 18 g/l; cholesterol: 7 mmol/l. Complement levels were in the normal range. She showed no evidence of weight gain or oedema. A percutaneous renal biopsy revealed minimal change disease without any significant deposit. No liver, spleen or lymph node enlargement was found. Abdominal ultrasound and excretory urography revealed no abnormality. The patient was treated by three infusions of prednisolone (5 mg/kg/dose): proteinuria remitted in 2 weeks. Steroids were witheld. Four weeks after, proteinuria recurred and progressive swelling of a left cervical adenopathy was noted. Further investigation disclosed mediastinal lymphadenopathy which was present on the first chest film, suggesting in retrospect that HD was present at the onset of the renal disorder. The patient was classified as stage II Bb (histiotype: mixed cellularity). Chemotherapy (2 MOPP/2 ABVD) followed by local irradiation was commenced and remission obtained. The urine became completely protein free in 3 weeks. Currently, after a 7.5 year follow up the patient shows no evidence of disease activity and no proteinuria.

Discussion

The literature suggests that the association of a NS and HD, although rare, is not fortuitous. The association does not significantly alter the prognosis for either of the two pathologies [1]. The course of the nephropathy does not always run parallel to that of the lymphoma [11]. No particular subset of patients with Hodgkin lymphoma has been shown to be especially susceptible to NS.

Table 1 Summary of data in cases of combined HD and NS in children. None of the 5 patients showed any evidence of renal compression and tumour infiltration with ultrasonographty. (*LM* light microscopy)

Case	Age (years) sex	HD localization	HD: Clinical stage and histology	Renal biopsy	Temporal link between HD and NS
1	10, M	Supraclavicular, mediastinum	II B b, nodular sclerosis (H2/1)	Normal (LM)	NS predated HD
2	14, F	Mediastinum	II B b, nodular sclerosis (H2/4S)	Mesangial hypercellularity IgM^+,$C1q^+$, $C3^+$	NS associated with HD activity
3	12, M	Mediastinum	IV B b, mixed cellularity (H3)	No	NS predated HD
4	12, M	Supraclavicular mediastinum	II B b, mixed cellularity (H3)	No	NS associated with HD activity
5	15, F	Cervical, mediastinum	II B b, mixed cellularity (H3)	Normal (LM)	NS associated with HD activity

Paraneoplastic glomerulopathy has also been reported in other malignancies that are uncommon in children (myeloma, carcinoma and Kaposi sarcoma) [2, 12], as well as in patients with Burkitt lymphoma [9], and Wilm tumour [8]. Minimal-change lesions are the most frequent in patients with HD, while membranous nephropathy is more suggestive of carcinoma, although there are many exceptions to this general rule. Lesions of membrano-proliferative and focal sclerotic nephropathy also occur concomitantly with miscellaneous tumours [5]. Amyloidosis is also one cause for glomerular lesions and NS in patients with advanced HD: their prognosis has been poor [21].

The temporal link between proteinuria and the malignancy was variable in the patients of this retrospective survey. In cases 1 and 3, as in other reported cases, NS predated the lymphoma by several months. The longest reported interval between these two events is 42 months [15].

The case 1 is similar to that of a 20-year-old patient described by Fouques et al. [6], and points to the responsability of immunosuppressive treatment in the pathogenesis of the lymphoma. It has clearly been demonstrated that immunosupressants can lead to lymphoproliferative diseases in organ transplant recipients [20], although most cases involve EBV+ non Hodgkin B cell lymphomas. The safety of CSA in the idiopathic nephrotic syndrome was recently analysed in 661 patients enrolled in 10 clinical studies [3]. Malignancies developed in five patients, including Hodgkin lymphoma in two. Case 1 may have had a subclinical lymphadenopathy (as for case 5) when he was initially seen for minimal-change nephropathy.

The association between this entity (HD+NS) and ITP has not been described, although auto-immunity and auto-immune syndromes have been linked with lymphoproliferative disorders [18]. Manifestations range from serum autoantibodies to auto-immune syndromes including cold urticaria, Raynaud disease, cold agglutinin disease, thyroiditis, and scleroderma, and generally precede the onset and diagnosis of these disorders.

The eight children of 15 years or less with combined HD and idiopathic NS reported since 1967 [5, 7, 10, 13, 16, 17] received either radiation therapy or nitrogen mustard, which led to the normalisation of proteinuria. When NS and HD develop concurrently, effective treatment of the HD results in remission of the NS, requiring no specific therapy directed at the renal lesion. The case 2 was unusual, as the proteinuria failed to remit when transient remission of the lymphoma was obtained following multidrug chemotherapy. In the case 1, the proteinuria relapsed despite partial control of HD after the first course of VBVP, but apparently responded to pefloxacin, suggesting that this antimicrobial agent may be useful for patients with a steroid-resistant NS [19].

The immunopathogical background of this entity is a mystery. The association of minimal-change NS with lymphoma supports a role for cells of the lymphoid system, or their products (lymphokines), as potential mediators of glomerular dysfunction in these disorders [14].

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