

Nephrotic syndrome and Hodgkin lymphoma in children. Report of two cases

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Abstract

Background: The association of nephrotic syndrome (NS) and Hodgkin's lymphoma (HL), although rare, is well recognised. In the majority of cases of HL, minimal change NS is detected.

Description of Cases: This report presents the occurrence of NS in two children with HL. In the first case, NS preceded the diagnosis of lymphoma by 3 months, while in the other child, the two disorders occurred simultaneously. In both cases, clinical manifestations and laboratory parameters (proteinuria) of NS resolved after effective treatment for active HL.

Conclusion: Prolonged proteinuria may be a paraneoplastic syndrome and HL should be considered in the diagnosis as it is crucial for the management of both entities. Hippokratia 2014; 18 (4): 373-375.

Keywords: Hodgkin, lymphoma, nephrotic syndrome, children, paraneoplastic

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Introduction

Paraneoplastic glomerulopathy has been reported in patients with malignancy¹. Nephrotic changes as part of the paraneoplastic syndrome are rare in lymphoid malignancies². In particular, the association of nephrotic syndrome (NS) with Hodgkin's Lymphoma (HL) is rare and there are few reports in the literature³⁻⁵. In the pediatric population an incidence of 1% has been described in France (5 patients out of 483 children with HL)⁶. Minimal change nephropathy is the most frequently observed renal lesion whereas this association appears, either simultaneously or within several months of each other^{2,3,5-7}. Two out of 87 children with HL seen in our unit over a period of 30 years, presented with NS and are described below. The diagnosis of HL was established in both children during their evaluation for nephrotic syndrome.

Case 1

A 14-year-old, adolescent girl was admitted because of periorbital and lower-extremities oedema, weight gain, proteinuria and increased erythrocyte sedimentation rate (ESR) of 145 mm/h. No lymph node, liver, or spleen enlargement was found. Kidney biopsy was not performed. With the diagnosis of NS, the initial treatment consisted of prednisone and, as a result, remission of proteinuria occurred in 2 weeks. Steroids were then withheld. She was re-admitted 3 months later for a relapse of proteinuria and elevated erythrocyte sedimentation rate (ESR) once again. A percutaneous renal biopsy was performed and the pathology examination revealed lesions of minimal change nephropathy. The chest radiograph (performed because of fever) showed several hilar and laterotracheal lymph nodes and diffuse patchy lesions in both lungs. At that time, a left

supraclavicular lymph node was palpable and the biopsy revealed the diagnosis of HL, stage IVB (because of the lung involvement) of nodular sclerosis type. According to the French Society of Pediatric Oncology protocol⁸, two cycles of OPPA (vincristine, prednisone, procarbazine, doxorubicin) plus four cycles of COPP (cyclophosphamide, vincristine, procarbazine, prednisone), followed by low-dose, involved-field irradiation 20 Gy to the neck and mediastinum (no lung irradiation because of excellent response), were commenced and remission of her lymphoma and nephropathy was obtained. Currently, 17 years off therapy, the patient remains in first complete remission of HL and shows no evidence of NS activity and proteinuria.

Case 2

A 5-year-old boy was admitted because of cervical and supraclavicular lymphadenopathy, periorbital oedema and an elevated ESR of 150 mm/h. Mediastinal widening and lung infiltrations were detected whereas a remarkable proteinuria was found. A diagnosis of mixed cellularity HL, stage IVB (due to lung involvement) was made after a lymph node biopsy was obtained. He received chemotherapy (2 OPPA / 4 COPP), as in the first case, followed by involved-field irradiation 20 Gy to the neck and mediastinum (no lung irradiation as above) and remission of his lymphoma and nephropathy was achieved. Currently, 6 years since the diagnosis, he is in complete remission whereas no signs of NS were found during the follow-up evaluations.

Discussion

NS and HL are considered to be linked. This association is rare in lymphoid malignancies and is mostly

observed in HL². In adult population the frequency of NS was found to be 0.4% among patients with HL⁴. However, the incidence of this association in children is not known. In two large series from France and Turkey the incidence of NS among HL patients was 1% and 0.6% respectively - 9 out of 1144 children with HL (0.8%) in both studies^{6,9}. In our department over a period of 30 years two cases of NS among 87 patients with HL have been depicted.

Although it has been reported that no particular subset of patients with HL are especially susceptible to NS, the mixed-cellularity and nodular sclerosis seem to be the predominant histology subtypes in both adults and children^{4,6,9}. In our two patients, diagnosis of HL of nodular sclerosis and mixed cellularity was respectively made.

In one of our patients who underwent a biopsy we detected the minimal-change-lesions type of NS. NS with minimal change lesions is the most frequent renal disease observed in patients with HL^{2,3}. In a literature review, Khositseth et al reported that other renal lesions associated with HL include membranous nephropathy, focal segmental glomerulosclerosis, mesangiocapillary glomerulonephritis, anti-glomerular basement membrane nephritis, and acute necrotizing glomerulonephritis¹⁰. In a recent study¹¹, Hanada et al reported 2 cases of nephrotic syndrome (membranous nephropathy) associated with B-cell non-HL and 1 case (minimal change disease) associated with HL. All three cases were characterized by glomerular endocapillary proliferation and massive glomerular infiltration of inflammatory cells.

The occurrence of nephrotic changes as manifestation of HL, suggests that some immunological abnormalities may play a role in the pathogenesis of this association. It is well known that autoimmune disorders have been linked to lymphomas¹². In the past, authors have suggested that T-lymphocyte function and Natural killer cell deficiency may lead to nephropathy in HL^{2,13}. Neuhaus et al suggest that lymphoid cells and lymphokines are potential mediators of glomerular dysfunction¹⁴. The role of cyclosporine A, which is used in steroid resistant nephrotic syndrome, in inducing HL in patients with idiopathic NS, should also be considered¹⁵. Audard et al, in a more recent study¹⁶, demonstrated for the first time, that c-maf inducing protein (c-mip) is selectively induced both in podocytes and in Hodgkin and Reed-Sternberg cells in patients with classical HL and minimal change NS but is not detected in patients with isolated classical HL, suggesting its potential involvement in the pathophysiology of this association.

The course of NS does not always run parallel to that of the lymphoma. According to a previous study of Audard et al¹⁷, approximately 43% of patients develop NS after the diagnosis of lymphoma, 38% before and 19% develop both diseases concurrently. In an already mentioned study, focused on childhood⁶, Stephan et al reported two children in which NS preceded the diagnosis of lymphoma by 6 months and 12 months respectively, while in three patients, the two disorders occurred simul-

taneously. Other authors have reported NS development 5 years after the remission of HL and 25 months before the relapse of the disease¹³. In our patients, NS preceded the HL diagnosis by 3 months in the first one, whereas in the second child the two disorders occurred simultaneously.

Another issue that has to be discussed is the prognosis of patients with a combination of NS and HL. When NS and HL develop concurrently, effective treatment of HL, results in remission of NS without a specific therapy directed at the renal lesion⁶. Our patients received adequate combined treatment for their lymphoma leading to disappearance of proteinuria and remain in remission for both HL and NS. Relapses of the NS usually coincided with a relapse of HL and responded to antineoplastic treatment³.

Conclusions

NS is a well recognised but rare entity in children with HL. Prolonged proteinuria may be a paraneoplastic syndrome and HL should be considered in the diagnosis. Concerning the prognosis, adequate and effective treatment of HL will result in remission of NS.

Conflict of interest

The authors have no conflicts of interest to declare.

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