Hodgkin's disease and renal paraneoplastic syndromes in childhood

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SUMMARY: Büyükpamukçu M, Hazar V, Tınaztepe K, Bakkaloğlu A, Akyüz C, Kutluk T. Hodgkin's disease and renal paraneoplastic syndromes in childhood. Turk J Pediatr 2000; 42: 109-114.

The purpose of this study was to investigate children followed as having both Hodgkin's disease (HD) and nephropathy and discuss the factors which might play roles in the pathogenesis of this association by reviewing the pertinent literature. Our experience among 661 children with HD revealed ten cases (1.5%) with nephropathy; eight of these were biopsy proven. Tissue diagnoses were amyloidosis (AA type) in four cases, and membranoproliferative glomerulonephritis and minimal change glomerulopathy in two cases each. Sex distribution was equal. There was a predominance of the mixed cellular (MC) histologic type in our patients with HD. Nephropathy was shown to antedate the diagnosis of HD in two cases and to herald a relapse in one. In brief, the development of a nephropathy in a patient with HD can be considered as a paraneoplastic phenomenon. Renal amyloidosis may already be present at the time of diagnosis of HD and must be kept in mind as a cause of proteinuria due to preexisting nephropathy. Developing renal paraneoplastic syndrome, even in early-staged HD, in children, may be a poor prognostic factor.

Key words: nephropathy, paraneoplastic phenomenon, childhood, Hodgkin's disease.

A relation between cancer and nephropathy manifested primarily by the nephrotic syndrome (NS) was first described by Galloway[1]. The incidence of Hodgkin's disease (HD) associated nephropathy is very low[2,3]. Minimal change nephropathy (lipoid nephrosis) is the most common (80%) renal lesion in patients with HD, while membranous glomerulopathy, membranoproliferative glomerulonephritis (MPGN), and focal sclerosis have also been reported in the literature[4-9]. Amyloidosis, also a rare cause of NS occurs in one to four percent of HD[6,9,10].

The purpose of this study was to investigate children followed as HD and nephropathy in Department of Pediatric Oncology of Hacettepe University Hospital and to discuss the factors which might play roles in its pathogenesis.

Material and Methods

Between October 1970 and January 1995, we recorded 661 biopsy-proven and subtyped patients with HD according to Rye modification of Lukes-Butler classification[11]; most were treated with combined chemotherapy (COPP-cyclophosphamide, vincristine, procarbazine, prednisolone; ABVD-adriamycin, bleomycin, vinblastine, dacarbazine) and radiotherapy (low-dose involved-field, 20-25 Gy) in the Department of Pediatric Oncology of Hacettepe University Hospital. Among these patients, there were only 10 patients with HD and nephropathy. Complete blood count, routine urine analysis, blood urea nitrogen (BUN), creatinine, uric acid, serum total protein, albumin, lipid, cholesterol, and qualitative and/or quantitative urine protein loss were investigated. Brief information about patients with nephropathy associated with HD is provided hereunder.

Cases 1 and 2

A 10-year-old boy and his seven-year-old sister were referred to our center in 1973 with twenty-four-and thirty-month histories of hematuria,

edema, decrease in urine output and multiple lymphadenopathy. They were diagnosed as HD, unclassified and lymphocyte depletion subtypes, respectively. Membranoproliferative glomerulonephritis accompanied HD was shown in their renal biopsies taken during staging laparotomy for HD. At that time there was no proteinuria andrenal function tests were in normal limits. Although MOPP (nitrogen mustard, vincristine, procarbazine and prednisolone) chemotherapy regimens were diministered, they died due to progressive HD at the 60th and 72nd months of HD diagnosis, respectively.

Case 3

A 12-year-old girl was referred to our center in 1978 with a seven-year history of HD (MC subtype diagnosis) and treatment with cyclophosphamide, procarbazine and prednisolone. She was treated with radiotherapy and several MOPP chemotherapy regimens for sternum involvement, and axillary and inguinal relapses. In the 10th year of HD diagnosis, she complained of a decrease in urine output and edema. Her biochemical results were BUN 10 mg/dl, creatinine 0.5 mg/dl, Na 133 mEq/L, K 3.5 mEq/L, total protein 5.1 g/dl, albumin 2.8 g/dl, cholesterol 210 mg/dl (N: 110-190 mg/dl), and qualitative and quantitative protein loss in urine 2+ and 46 mg/h/m^2, respectively. Amyloidosis was revealed in the needle biopsy from kidney. She died in a short time after biopsy due to renal insufficiency.

Case 4

A 15-year-old-boy was hospitalized for bilateral enlarged cervical lymph nodes and pretibial edema in 1983. He was diagnosed as HD, lymphocyte predominance subtype, from cervical biopsy. After clinical staging he was stage II. His biochemical data were as follows: BUN 14 mg/dl, creatinine 0.5 mg/dl, Na 132 mEq/L, K 4.2 mEq/L, total protein 4.7 g/dl, albumin 1.8 g/dl, total lipid 1840 mg/dl (N: 400-900 mg/dl), cholesterol 380 mg/dl, and protein loss in urine qualitatively 3+ and quantitatively 41.6 mg/h/m^2. He was treated with cyclophosphamide, vincristine, procarbazine and prednisolone (COPP) and low-dose involved-field radiotherapy. He succumbed from varicella infection thirteen months after diagnosis of HD and NS while neither was in remission.

Case 5

A seven-year-old boy presented with bilateral cervical bulky mass and generalized edema in 1984. He had undergone biopsy from cervical mass at another health center and was reported as HD (MC subtype) one year before admission to our hospital. After histopathological confirmation and clinical staging investigations he was found to have stage II_B disease. The results of the biochemical analyses were as follows: BUN 10 mg/dl, creatinine 0.5 mg/dl, Na 131 mEq/L, K 3.2 mEq/L, total protein 4.6 g/dl, albumin 2.8 g/dl, total lipid 940 mg/dl, cholesterol 210 mg/dl, and quantitative protein loss in urine 4+. He was treated with COPP and low-dose involved-field radiotherapy. He was lost to follow-up eight months after HD diagnosis while both HD and NS were in remission.

Case 6

A 16-year-old boy was referred to our hospital in 1985 with the complaints of weight loss, fever, night sweating, diarrhea and abdominal pain. He had been given COPP chemotherapy regimen for HD, MC subtype, stage IV_B at another health center for two years, after which ABVD (adriamycin, bleomycin, vinblastine and dacarbazine) regimen was started because of relapse. He was treated with ABVD and some other chemotherapy regimens including cisplatin, VP16, CCNU, prednisolone and mantle and inverted Y rediotherapy because of intractable systemic disease. At the 60th month of diagnosis, massive proteinuria (58.0 mg/h/m^2), hypoalbuminemia (2.6 g/dl), and edema developed. At that time, HD was localized on spleen only by radioimaging techniques. Amyloidosis accompanied with HD was shown in the specimens which were taken during splenectomy of abdominal lymph nodes, spleen, liver, and kidney. He died due to systemic disease 79 months after the diagnosis of HD.

Case 7

A six-year-old boy was admitted to our hospital in 1987 with loss of appetite, abdominal distension, and dyspnea. On his chest x-rays there was a mediastinal mass. He was diagnosed as HD (MC subtype) by thoracotomy. After clinical staging procedures, he was accepted as stage IV_A. At the time of diagnosis, his renal function tests were in normal limits. After COPP and low-dose involved-field radiotherapy he was in remission

but relapsed one year later. He was then given ABVD regimen. Proteinuria (qualitatively 4+, guantitatively 43.2 mg/h/m^2), hypoalbuminemia (2.0 g/dl), hypercholesterolemia (590 mg/dl) and edema developed 72 months after HD diagnosis as HD was in remission. Needle biopsy showed minimal change nephropathy. NS was successfully treated with short-term corticosteroid, but systemic relapse was later determined. High-dose chemotherapy with peripheral stem cell rescue was performed. He is alive without disease ten years from the time of HD diagnosis.

Case 8

A seven-year-old girl with a one-year history of cervical lymphadenopathy was admitted to hospital because of generalized edema in 1989. On her physical examination, a right cervical 3x2 cm lymph node and 2+ pretibal edema were determined. Excisional biopsy from cervical lymph node was reported as HD. MC subtype, including amyloid deposition. After clinical staging she was accepted as stage II_A. Her biochemical results were as follows: BUN 10 mg/dl, creatinine 0.5 mg/dl, Na 120 mEq/L, K 2.7 mEq/L, total protein 4.1 g/dl, albumin 1.0 g/dl, cholesterol 206 mg/dl, and protein loss in urine qualitatively 4+ and quantitatively 42.1 mg/h/m^2. She died within one month because of adrenal insufficiency. Amyloidosis was shown in necropsy materials from adrenal glands and kidneys.

Case 9

A seven-year-old girl was admitted to the hospital in 1989 with the complaints of fever, weight loss, a mass localized on the left paravertebral region and edema. On her examination there were bilateral multiple microlymphadenopathies, hepatosplenomegaly, left paravertebral mass (6x7 cm) and pretibial edema. Biochemistry analyses were BUN 10 mg/dl, creatinine 0.4 mg/dl, Na 129 mEq/L, K 2.8 mEq/L, total protein 6.0 g/dl, albumin 1.1 g/dl, cholesterol 314 mg/dl, and protein loss in urine qualitatively 3+, and quantitatively 35.8 mg/h/m^2. Renal needle biopsy demonstrated the presence of amyloidosis at the time of diagnosis. After biopsy from the mass she was treated with ABVD for the diagnosis of HD, nodular sclerosing subtype, stage IV_B. She was lost to follow-up 14 months after diagnosis while HD was in remission and NS in the active phase.

Case 10

A 15-year-old girl presented in 1989 with a history of fever, weight loss, dyspnea, cough and pretibial edema. Supraclavicular lymph node biopsy was reported as HD, MC subtype. Bilateral renomegaly was determined on abdominal ultrasonography. The results of the biochemistry were BUN 12 mg/dl, creatinine 0.7 mg/dl, Na 135 mEq/L, K 4.0 mEq/L, total protein 5.9 g/dl, albumin 1.8 g/dl, and spot urine protein/creatinine 4. Renal needle biopsy was performed and minimal change nephropathy was reported. After clinical staging she was stage IV_B and started on COPP regimen. She died due to neutropenic sepsis one month after diagnosis.

Results

Of 661 patients with HD, 10 patients with a median age of seven were determined to have associated renal pathology consisting of four amyloidosis, two minimal change nephropathy, and two MPGN. Two patients had nephrotic syndrome clinically but no renal biopsy was performed (Cases 4 and 5). The sex distribution was equal. While four patients were early-staged (stages I-II) HD, the others were advanced-staged (stages III-IV). Of 10 patients, only four had systemic symptoms for HD. While Cases 4, 9 and 10 had NS at the time of diagnosis. NS developed after diagnosis of HD in Cases 3, 5, 6, 7 and 8 (range 12-120 months). NS heralded the relapse in Case 7 who was previously in full remission; in Cases 1 and 2 NS had never been observed. All patients in the group in which nephropathy developed after the diagnosis of HD, except Case 7, had active HD at the beginning of nephropathy. Clinical and pathological features of the patients are shown in Table I.

Discussion

Tumors can produce signs and symptoms independent from tumor mass or metastases. These are collectively referred to as "paraneoplastic syndromes". Although association between HD and nephropathies is well-known, it is relatively rare. In a collection of more than 1,700 patients with HD in the literature only nine (0.5%) had nephropathy[12,13]. In our patients with HD, renal paraneoplastic syndromes were found in 1.5 percent. Although the most frequently seen renal pathology in patients with HD is reported as minimal change nephropathy (MCN) in the

Table I. Clinical and Pathologic Features of Hodgkin's Patients with Nephropathy

Case No.	Age (Years)-Sex (Onset of HD)	Type of HD	Stage	Onset of nephropathy* (months)	Type of renal pathology	Diagnostic approach	Follow up and end results (months)
1	10 M	UC	IV_A	-30	MPGN	Incisional biopsy	Exitus in 60 mo.
2	7 F	LD	IV_A	-24	MPGN	Incisional biopsy	Exitus in 72 mo.
3	5 F	MC	II_A	120	Amyloidosis	Needle biopsy	Exitus in 156 mo.
4	15 M	LP	II_A	0	NS	Clinical and Lab.	Exitus in 13 mo.
5	6 M	MC	II_B	12	NS	Clinical and Lab.	Lost to follop-up in 18 mo.
6	14 M	MC	IV_B	60	Amyloidosis	Incisional biopsy	Exitus in 79 mo.
7	6 M	MC	IV_A	72	MCN	Needle biopsy	Alive in 120 mo.
8	7 F	MC	II_A	12	Amyloidosis	Necropsy	Exitus in 1 mo.
9	7 F	NS	IV_B	0	Amyloidosis	Needle biopsy	Lost to follow-up in 14 mo.
10	15 F	MC	IV_B	0	MCN	Needle biopsy	Exitus in 1 mo.

LP : Lymphocyte predominance.
MC : Mixed cellularity.
UC : Unclassified.
MPGN: Membranoproliferative glomerulonephritis.
NS : Nodular sclerosing.
LD : Lymphocyte depletion.
MCN: Minimal change nephropathy.
NS : Nephrotic syndrome.
* Onset of nephropathy vs. onset of HD.

literature, in which the study population had both adult and pediatric patients, only two of eight biopsy-diagnosed cases in the presented pediatric series were observed as MCN[4,5,7]. It was thought that the defect in T lymphocyte function, known to be present in patients with HD, with the elaboration of proteases or lymphokines that alter the selectivity characteristics of the glomerular basement membrane, may play a role in the etiopathogenesis of MCN, although a scientific basis for such a scenario has not emerged[14,15]. It has also been postulated that loss of immunoregulatory functions of arachidonic acid metabolities contributes to the increased glomerular permeability[16]. Unfortunately, we did not study T lymphoycte functions or cytokines in our patients.

Independent of tumor mass or metastases, most patients with a variety of neoplastic diseases are exposed to continuous antigenemia such as tumor-associated antigens, reexpressed fetal antigens, viral antigens and so on[3,14]. These antigens stimulate antibody production and form circulating immune complexes and antiideotypic cryoimmunoglobulins. In many instances these immune reactants are deposited or formed in situ in the glomerular mesangium and capillary walls[8]. Thus glomerulopathies due to immune complexes occur. But NS may not always occur in renal paraneoplastic syndrome due to immune complexes in HD. We did not observe NS in our patients with MPGN. Electronmicroscopic studies were not done in our cases (Cases 1 and 2). Immunopathologic data of renal paraneoplastic cases were reported in detail by Tınaztepe et al[17-19].

Although there is no concensus that age, sex and stage of HD have a bearing on the appearance of renal paraneoplastic syndrome, some authors believe that prevalence of glomerulopathies during the course of HD is greater in males[7,20]. We found that neither age (range: 5-15), sex (5 male, 5 female) nor stage (from IA to IVB) had any predominancy in our patients. But as it is reported being more prone to develop in histologic type of mixed cellularity (MC), half of our patients whose type of HD was specified had MC subtype.

Nephropathy has been shown to antedate the diagnosis of HD or to herald a relapse as seen in our Cases 7, 8 and 9[20-22]. Though Egan and Lewis[3] mentioned that NS in association with HD was rather resistant to the usual modes of treatment of MCN. Case 7, in whom NS heralded a relapse, was treated using prednisolone with a good response. The other case of MCN was remitted by chemotherapy and radiotherapy.

Although amyloidosis is usually seen in nonmalignant diseases, it may accompany HD in childhood[6]. Amyloidosis shown in HD is secondary amyloidosis due to AA protein deposits[6,23]. Amyloid deposits seen in HD can occur in various organs and tissues throughout

the body as in renal cell carcinoma[24]. So one possible mechanism for amyloid production in HD may be one of those seen in renal cell carcinoma: the tumor cells either secrete an amyloidogenic substance or modify by partial proteolysis a serum precursor protein, serum amyloid A protein (SAA), into an amyloidogenic fragment[24]. A second and more likely mechanism involves a stimulus by the tumor to produce SAA protein by monocyte-phagocyte system. SAA is one of the most dramatic forms of acute phase reactants. The production of this protein is altered tremendously (increased greater than 1,000 fold) in response to some cytokines causing inflammation and necrosis[25,26]. Cytokines and acute phase proteins produced by Hodgkin's cells are well-known[27]. Consequently, it may be thought that many cytokines, playing a role in both production of acute phase proteins and inflammatory response, are stimulated to release by Hodgkin's cells. All of them may cause a stimulus to production of SAA protein. Although some authors believe Hodgkin's disease-associated amyloidosis is the consequence of a long-standing insufficiently treated disease, two of our patients were shown to have amyloidosis at the time of diagnosis of HD[9]. It may be that there is a correlation between the power of antigenic stimulation and formation of amyloidosis or that there is a factor contributing to the development of both amyloidosis and HD and appearing before the detection of HD.

Overall survial rates in our institution were 94.7 and 74.6 percent at 10 years for patients with HD without renal paraneoplastic syndrome in stages I-II and stages III-IV, respectively[28]. But seven of the patients with renal paraneoplastic syndrome secondary to HD, three of whom had early-staged HD, died. Therefore, renal paraneoplastic syndrome, even in an early stage, may be a poor prognostic factor.

In conclusion, the development of a nephropathy in a patient with HD can be considered as a paraneoplastic phenomenon. Its incidence is actually very low. Amyloidosis must be kept in mind as a cause of NS associated with HD. Although it is thought that Hodgkin's disease-associated amyloidosis is a consequence of long-standing HD, it may be seen at the time of diagnosis of HD, as in two of our patients. Developing renal paraneoplastic syndrome, even in early-staged HD, in children, may be a poor prognostic factor.

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