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SHORT COMMUNICATIONS AND CASE REPORTS

A patient with diffuse large B-cell non-Hodgkin's lymphoma and AA type amyloidosis

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Summary

AA-type amyloidosis is a consequence of a long-standing systemic inflammation and is not associated with a monoclonal protein or clonal bone marrow plasma cells. Proinflammatory cytokines such as interleukin (IL)1, IL-6, and tumor necrosis factor (TNF) stimulate the synthesis of serum amyloid A during inflammation. Although the association of non-Hodgkin's lymphoma (NHL) with AL-type amyloidosis is well known and patients with Hodgkin's lymphoma with AA amyloidosis have been described, AA-type amyloidosis with NHL is extremely infrequent. We report a case of amyloidosis associated with NHL that subsided during R-CHOP chemotherapy.

Key words: AA amyloidosis, amyloidosis, diabetes mellitus type 2, diffuse large B-cell lymphoma, non-Hodgkin's lymphoma

Introduction

Amyloidosis results from the accumulation of insoluble amyloid proteins, mainly in the extracellular spaces of tissues. Amyloid fibrils can be deposited locally or may involve virtually every organ system of the body and may have no apparent clinical consequences or may lead to severe pathophysiologic changes, so the symptoms from the different organs vary from patient to patient. The clinical diagnosis of amyloidosis is usually not made until the disease is far advanced because of nonspecific symptoms and signs. Amyloidoses are classified according to the biochemical nature of the fibril-forming protein. AL amyloidosis is immunoglobulin light-chain-derived and a clonal plasma cell disorder always exists. Mature B lymphocytes are destined to produce antibodies. Under normal circumstances, maturation to antibody-secreting plasma cells is stimulated by exposure to the antigen for which the surface immunoglobulin is specific; however, in the plasma cell disorders, the control over this process is lost. AA amyloidosis is a consequence of a long-standing systemic inflammation and is not associated with a monoclonal protein or clonal bone marrow plasma cells. During inflammation, proinflammatory cytokines such as IL-1, IL-6, and TNF stimulate the synthesis of serum amyloid A [1-6]. Localized or organ-limited amyloidoses are associated with aging and diabetes, and may occur in isolated organs without evidence of systemic involvement.

Amyloidosis is a rare complication of lymphomas. Although the association of NHL with AL amyloidosis is well known [7-11] and patients with Hodgkin's lymphoma have been described as having AA [12-14], AA-type amyloidosis with NHL is extremely infrequent [15-17].

Herein, we report the case of a woman with AA-type amyloidosis and diffuse large B-cell lymphoma (DLBCL).

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Case presentation

A 51-year-old female was admitted to the Hematology Department with anemia and hepatosplenomegaly that had been established when she had been hospitalized for urinary tract infection one month ago. Her past medical history included diabetes mellitus type 2 and thalassemia trait diagnosed years ago. She did not take any medication. Her physical examination revealed hepatosplenomegaly but she had no peripheral lymphadenopathy. Laboratory findings were as follows: hypochromic microcytic anemia (Hb 9.4 g/dL and MCV 55.9 flt), leukocytosis (WBC 25.800/μL) and a slightly elevated erythrocyte sedimentation rate (43 mm/h). Her peripheral blood smear showed 65% neutrophils, 30% lymphocytes and 5% monocytes. Beta-2-microglobulin level was 5.6 mg/dl (normal 0.6-3.80). Renal function tests, liver enzymes and lactate dehydrogenase level were all within normal limits. Right pleural effusion was identified on the posteroanterior chest x-ray (Figure 1), and on abdominal CT scan there were enlargement of the tail of the pancreas, inhomogeneous retroperitoneal fatty tissue and lymphadenopathy of the paraaortic and paracaval regions, near to celiac truncus, and splenomegaly with hypoechoic lesions. Doppler ultrasonographic examination of the portal system was performed and showed normal blood flow of splenic and portal veins. On diagnostic laparotomy, liver biopsy, splenectomy and diagnostic lymph nodes sampling were performed. Histological examination of the nodular lesions in the spleen and lymph nodes showed a diffuse infiltrate of large centrocytes and centroblast-like neoplastic lymphoid cells. Immunohistochemistry showed that the neoplastic lymphoid cells were CD20 and CD79a positive, but negative for CD3, CD10 and CD30. Based on the morphologic and immunophenotypic findings, a diagnosis of diffuse large peripheral B-cell NHL was established. There was no lymphoid infiltration on liver biopsy, but the walls of the liver vessels were thickened, indicating deposition of an abnormal substance (Figure 2). Biopsy of the rectal mucosa was also performed (Figure 3A) which revealed AA-type amyloid deposition in the walls of small vessels demonstrated by immunohistochemistry also (Figure 3B). Deposition of amyloid on the vessels' wall was confirmed by Congo red staining (Figure 3C).

After a peak seen in the gamma region on serum protein electrophoresis, both serum and urine immunofixation were performed but no monoclonal protein was detected. Serum concentrations of IgG, IgM, IgA and IgE were within normal limits. M-mode and Doppler echocardiography were normal.

Six cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) combination chemotherapy were administered. After the completion of therapy the patient was reevaluated. Thoracic and abdominal CT revealed complete response; pleural effusion and nodal disease disappeared and the pancreas returned to normal size and appearance. Biopsy of the rectal mucosa was performed again and pathological examination showed no amyloid deposition.

Discussion

Although the association of NHL with AL amyloidosis is well known [7-11], amyloidosis is a rare complication of lymphomas, and AA-type amyloidosis with NHL is extremely infrequent [15,16]. In

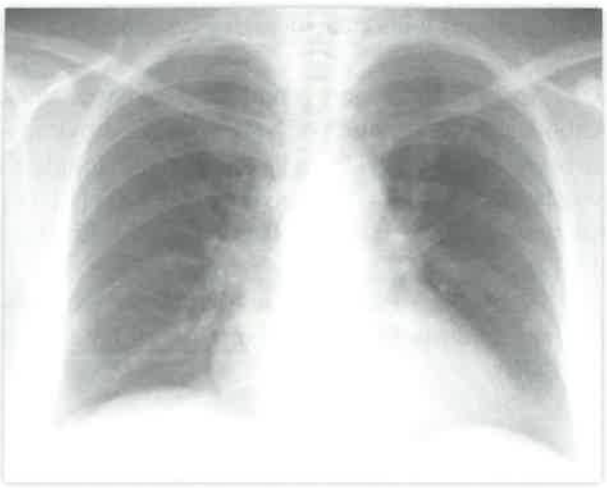


Figure 1. Posteroanterior chest x-ray with right sided pleural effusion.

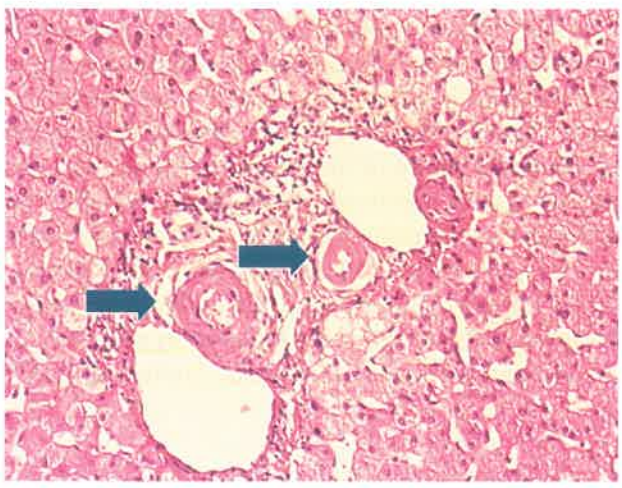


Figure 2. Deposition of amyloid on the walls of liver blood vessels (arrows) (H&E×200).

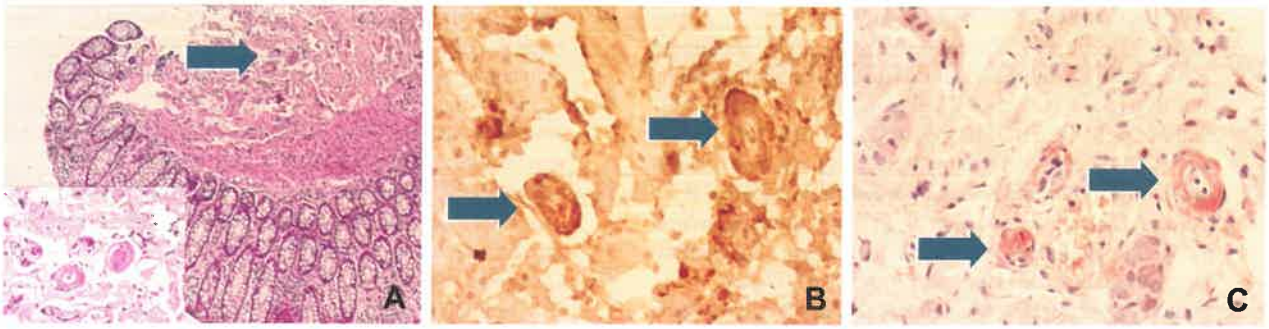


Figure 3. A: Rectal mucosa showing homogeneous amyloid deposition in the walls of vessels (arrow) (H&E×40; Inset H&E×200); B: immunohistochemistry (×200) and C: Congo red stains of the vessels (arrows) (×100).

particular, lymphoplasmocytoid (LPL) and marginal zone lymphomas (MZL) are associated with amyloidosis [7-11,18-21]. Both LPLs and MZLs are indolent disorders that may synthesize heavy and light chain molecules [22-24].

In most of the cases the underlying etiology of AA amyloidosis is clear and usually is present for many years.

In our case, although the patient had an urinary tract infection in the last month, and a lobulated and small right kidney delineated by ultrasonography had implied a chronic urinary tract infection, the history of the patient was not consistent with a recurrent or chronic urinary tract infection.

The patient with diffuse large B-cell NHL reported by Xicoy and colleagues had a partial remission after 6 cycles of CHOP chemotherapy and she had been diagnosed with AA amyloidosis with biopsies from the residual mass in the abdomen [15]. Congo red stain on the first liver biopsy also showed that amyloidosis was present at the time of NHL diagnosis. But this feature could not rule out the possibility that the patient had an AA-type amyloidosis previous to the development of NHL, like our patient. Similarly to our patient, she did not have an obvious cause of AA amyloidosis. In the second case report by Zhu and colleagues, there was also no apparent cause of AA amyloidosis other than follicular NHL which existed for 4.5 years [16]. Our patient had been diagnosed with AA amyloidosis before initiation of chemotherapy.

The features and clinical course of amyloidosis associated with NHL are not well characterized, and the diagnostic approach and optimal therapy remain undefined. However, rituximab has significant activity in LPL/Waldenström's macroglobulinaemia [8,25] and other low-grade NHL, so it may be effective especially in AL amyloidosis which is associated with NHL.

In our case, regarding the very short time which was not long enough for the development of amyloidosis, it was very unlikely that amyloidosis was due to DLBCL. Interestingly enough, the symptoms and findings of DLBCL and AA amyloidosis subsided together with R-CHOP chemotherapy. It is unlikely that the pancreatic islet cells that secrete localized islet amyloid polypeptide as seen in diabetic patients, or hepatocytes that secrete serum amyloid A in an inflammatory disorder would be affected by R-CHOP chemotherapy. It can be said that complete remission of the NHL resulted in the resolution of amyloidosis. In conclusion, although it is very unlikely, one can say that AA amyloidosis in our case was associated with DLBCL and this was the second reported case.

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