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CLINICAL INVESTIGATION

Diagnostic value of bone marrow biopsy in patients with renal disease secondary to familial Mediterranean fever

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Diagnostic value of bone marrow biopsy in patients with renal disease secondary to familial Mediterranean fever. Systemic AA type amyloidosis with renal involvement is the major cause of morbidity and mortality in patients with familial Mediterranean fever (FMF). A histopathological examination is essential to achieve a definite diagnosis in systemic amyloidosis. The diagnostic yield of the procedure varies according to the biopsy site and renal biopsy has the highest yield. On the other hand this procedure has its own complications and requires hospitalization of the patient. Alternative biopsy sites have been proposed with varying degrees of sensitivity and morbidity to reduce the morbidity and mortality of solid organ biopsies. We performed bone marrow biopsies in 39 patients with FMF who had different stages of renal disease. Thirty-one (79.5%) of the 39 specimens showed significant perivascular amyloid infiltration when stained with crystal violet and Congo red. An immunoperoxidase stain with a monoclonal antibody proved that these deposits were AA type amyloid. We suggest that bone marrow biopsy can be utilized for a safe and quick diagnosis of systemic amyloidosis in patients with FMF and renal disease.

Familial Mediterannean fever, which is an autosomally recessive disorder affecting several ethnic groups in Middle East and Mediterranean countries, is characterized by a high incidence (60%) of AA-type systemic amyloidosis and is a common cause of end-stage renal disease in the Turkish population [1]. Clinical course of renal amyloidosis usually follows a step-wise progression, extending from asymptomatic proteinuria to end-stage renal disease. Renal failure is the leading cause of morbidity and mortality in patients with FMF [2]. Studies of the last decade have enabled us to differentiate different forms of protein components leading to amyloid deposition [3]. These advances in amyloid research will provide new diagnostic and therapeutic approaches, but two fundamental issues of amyloidosis remain unchanged: (1) The precursor protein may vary but the eventual point is the deposition of amyloid fibrils around the walls of small blood vessels; (2) A histopathological examination is required for a definite diagnosis [4]. Several biopsy sites with different sensitivities have been proposed to diagnose AA amyloidosis with renal involvement and patients with systemic amyloidosis are at increased risk for hemorrhagic complications after solid organ biopsies because of their well-defined coagulation defects [5]. Bone marrow is abundant in small blood vessels and reticuloendothelial cells, and it has been shown that amyloid deposition in the bone marrow can be detected in 30 to 50% of patients with primary amyloidosis [6].

The aim of this study was to evaluate the diagnostic yield of bone marrow biopsy in patients with clinically overt renal disease due to FMF in order to offer a safe, quick and sensitive diagnostic approach.

Methods

Clinical features

Thirty-nine patients with FMF and renal disease were evaluated in the Nephrology Unit of Hacettepe University, School of Medicine, Ankara. Twenty-five of them were registered in the FMF Registry Group of Hacettepe University Hospital, Departments of Pediatrics and Internal Medicine. A positive family history and typical progression of the disease was noticed in their childhood, and elevation of fibrinogen levels and other acute phase reactants together with leukocytosis during acute attacks were also observed. These patients were prescribed colchicine and offered a follow-up program but were not compliant with their treatment and program. The other 14 patients also had a positive family history and characteristic clinical and laboratory findings, but were referred to our hospital after developing renal complications. Twenty were male and 19 female, with an average age of 29 ± 4. Twenty patients (51.3%) had nephrotic syndrome with creatinine clearance values over 60 ml/min, 15 patients (38.5%) had chronic renal failure with creatinine clearance values below 30 ml/min and four patients (10.3%) were on a regular dialysis program. Fourteen patients had a previous histopathological diagnosis with a renal biopsy and 11 patients with a rectal biopsy. In the remaining 14 patients a histopathological examination had not been performed before.

Laboratory data

Twenty-five patients (64.1%) had enlarged kidneys and 12 (30.8) had normal sized kidneys on ultrasonographic examination. Two patients on the regular dialysis program had bilateral contracted kidneys which also had cyst formation. All of the patients were anemic and their mean hemoglobin and

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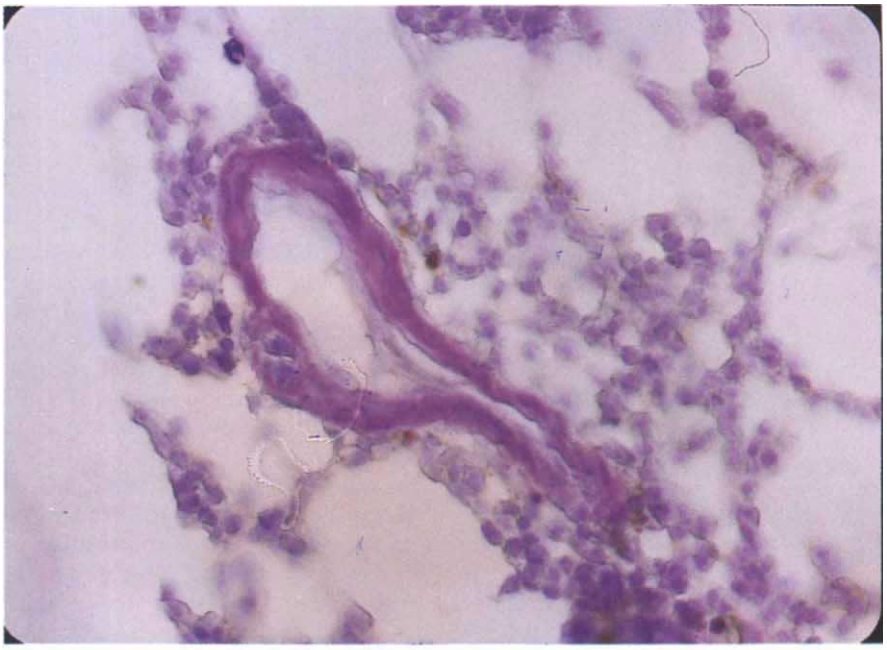

Fig. 1. *Amyloid deposition around a blood vessel.* Bone marrow biopsy (Crystal violet, × 230). Publication of Figures 1, 2, and 3 in color was made possible by a joint grant from Dako (Glastrup, Denmark) and the International Society of Nephrology.

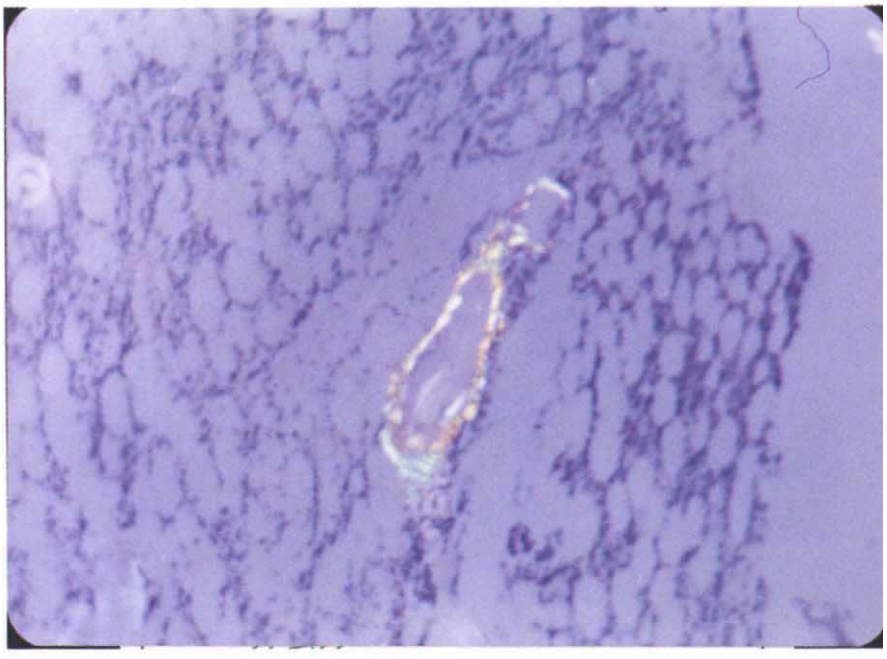

Fig. 2. *Birefrigerence under polarized light of amyloid deposits in the bone marrow (Congo red, × 115).*

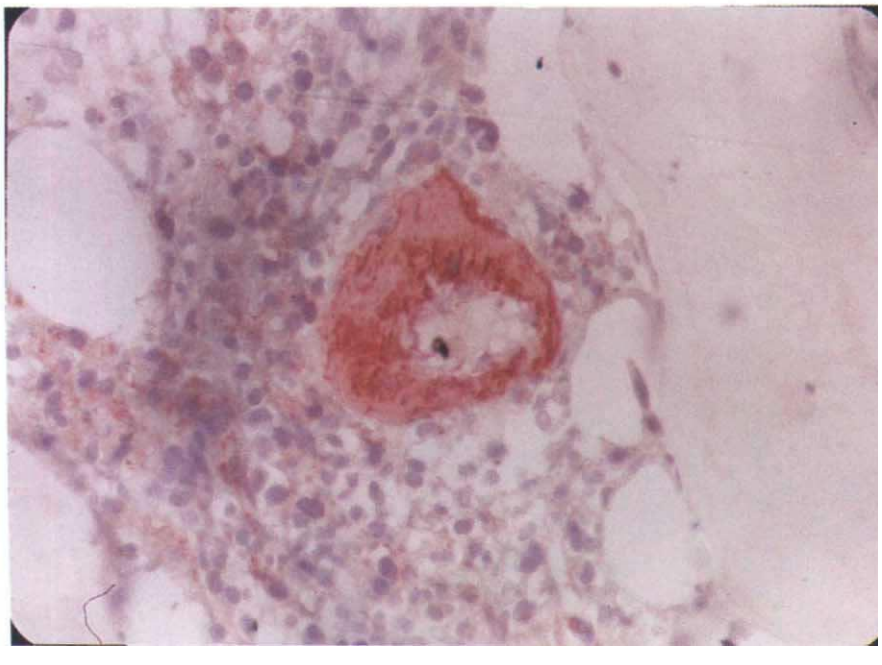

Fig. 3. *Immunoperoxidase stain for AA type amyloid (Streptavidin-biotin complex × 460).*

Table 1. Diagnostic value of bone marrow biopsy in the detection of AA type amyloidosis in 39 patients with FMF and renal disease

	NS	CRF	ESRD	Total *N*	Yield %
Initial bone marrow biopsy	7	4	—	14	78.6
Patients with a previous positive biopsy					
Rectal	3	4	4	11	
Bone marrow	3	3	3	14	81.8
Renal	7	5	2		
Bone marrow	7	3	1		78.6

Abbreviations are: NS, nephrotic syndrome; CRF, chronic renal failure; ESRD, end-stage renal disease.

hematocrit values were 9.4 ± 2 g/dl and 26 ± 2%, respectively. No evidence of urinary monoclonal light chain excretion was observed by immunoelectrophoresis.

Pathological methods

Posterior superior iliac crest was the preferred biopsy site and the specimens were obtained with a modified Jamshidi needle as an outpatient procedure. No complications were observed. Bone marrow biopsies averaging 10 mm in length were decalcified and stained with hematoxylin eosin (H + E), crystal violet and Congo red in the Pathology Department, and examinations were made with light microscopy and under polarized light. In order to prove that amyloid deposits were AA type, an immunoperoxidase (avidin-biotin) staining with a monoclonal antibody against AA type amyloid (DAKO) was used. The sections were regarded as inadequate if they did not contain at least three blood vessels.

Results

In 31 of 39 patients with FMF and renal disease (79.5%) amyloid deposits were detected around the blood vessels in the bone marrow biopsies. There was a complete correlation of crystal violet and Congo red stains, and all of the 31 specimens were positive for amyloid with both of these stains (Figs. 1 and 2). Immunoperoxidase staining proved that the deposits were AA type amyloid in these 31 patients (Fig. 3). Thirty-nine of the bone marrow biopsies were normocellular and seven showed slight erythroid hyperplasia. Plasmacytosis and presence of atypical plasma cells were not detected in any of these 39 patients. In two of the patients on regular dialysis, three of the patients with chronic renal failure and three patients with nephrotic syndrome, bone marrow examinations failed to demonstrate amyloid deposition. In one patient with nephrotic syndrome a rectal biopsy demonstrated the presence of amyloid deposition, while in two patients rectal biopsies were also negative and renal biopsies yielded the diagnosis. The other four patients had been subject to renal biopsies before, which demonstrated renal amyloidosis.

In 14 of the patients without a previous biopsy, 11 specimens demonstrated amyloid deposition in the bone marrow (78.6%). Four of these patients had chronic renal failure and seven had nephrotic syndrome. Rectal biopsies of the remaining two patients with nephrotic syndrome were also negative and the diagnosis was achieved by a renal biopsy as mentioned above. These findings are summarized in Table 1.

Discussion

Bone marrow biopsy has a diagnostic yield of 30 to 50% in patients with AL type primary amyloidosis and may be referred as the initial diagnostic site [7, 8]. On the other hand, subcutaneous fat aspiration, gingiva and rectal biopsies are employed in the diagnosis of AA amyloidosis secondary to FMF with renal involvement, if solid organ biopsy is contraindicated [9]. Rectal biopsy has a diagnostic yield of 75 to 85% if an adequate submucosal specimen is obtained but is also associated with a bleeding risk and bacteremia [10]. It also requires an endoscopic procedure done by a skilled endoscopist and may cause patient discomfort. This study suggests that bone marrow biopsy has an overall diagnostic yield in the diagnosis of AA type systemic amyloidosis in 79.5% of patients with overt clinical renal disease in patients with FMF. Furthermore, it provided an initial diagnosis of AA type systemic amyloidosis in 11 of 14 patients (78.6%). Percutaneous bone marrow biopsy is a safe method and can be performed as an outpatient procedure. The biopsy procedure does not require specialized instruments and personnel. This diagnostic approach cannot detect immune mediated glomerular diseases which are common in some ethnic groups with FMF [11]. On the other hand, it has the advantage of providing data about the hematologic profile of these patients with renal disease and may be helpful for issues such as: response to colchicine, monitorization of erythropoietin treatment, detection of macrophage iron stores and aluminum toxicity. The diagnostic value of bone marrow biopsy in earlier stages of the disease, when clinical signs of renal amyloidosis are not evident, is yet to be determined.

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