Nail Biopsy in the Diagnosis of Systemic Amyloidosis

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ABSTRACT

A 60-year-old woman with a 13-year history of monoclonal gammopathy of unknown significance (MGUS) presented with worsening nail dystrophy. Prior workup for systemic amyloidosis had been unrevealing, and no other signs of cutaneous disease were present. Nail biopsy was consistent with amyloid deposition, and the patient subsequently underwent autologous hematopoietic stem cell transplantation for AL amyloidosis. In light of the growing literature regarding nail changes as a presenting sign of systemic amyloidosis and the promising utility of nail biopsy, we suggest a low threshold for biopsy in appropriate patients when nail changes characteristic of amyloidosis are refractory to conventional treatment.

INTRODUCTION

Amyloidosis is characterized by the extracellular deposition of insoluble fibrillary proteins. AL amyloidosis (or primary amyloidosis) involves the deposition of amyloid light-chain due to an underlying plasma cell dyscrasia, while AA amyloidosis (or secondary amyloidosis) involves the deposition of serum amyloid A, most often due to a chronic inflammatory condition. Cutaneous manifestations of amyloidosis, seen in almost half of patients, classically include purpura, ecchymoses, petechiae, and waxy papules and nodules. We present a case in which dystrophic nail changes were the sole presenting sign of AL amyloidosis.

CASE REPORT

A 60-year-old woman with common variable immunodeficiency and a 13-year history of IgG monoclonal gammopathy of undetermined significance (MGUS) was seen in clinic due to nail changes of six months’ duration. Examination of the fingernails demonstrated distal nicking and onycholysis, as well as onychorrhexis and slight swelling of the proximal nail folds (Figure 1). The toenails showed signs of fungal infection but no other changes, and her dermatologic exam was otherwise unremarkable.

On follow up four months later, the patient described increased tenderness of her fingernails while doing housework. Examination showed worsening of her nail...
changes, and a 4 mm punch biopsy of the left thumb nail matrix was performed. On H&E, the biopsy showed dull pink globules filling widened papillae within the nail matrix. Staining with crystal violet and PAS (Figure 2) were consistent with amyloid deposition.

At the time of initial presentation to our clinic, the patient was asymptomatic and abdominal fat pad biopsy, skeletal surveys, and cardiac magnetic resonance imaging had been unremarkable. She was being observed without therapy by her oncologist. Following the nail biopsy, repeat abdominal fat pad biopsy was positive for amyloid deposition, though the skeletal survey and cardiac workup remained unremarkable. Bone biopsy showed 5 percent monoclonal plasma cells and no amyloid. The patient was diagnosed with AL amyloidosis and underwent autologous hematopoietic stem cell transplantation within three months of her nail biopsy.

![Figure 1. Nail dystrophy consistent with amyloidosis. Distal nicking, onychorrhexis, and slight swelling of the proximal nail folds are seen.](image1)

![Figure 2. PAS stain of the nail matrix. Positive PAS staining is consistent with amyloid deposition.](image2)

**DISCUSSION**

Diagnosis of systemic amyloidosis remains challenging because its presentation depends on the organ system(s) affected and is often nonspecific. Moreover, confirmation of amyloid on tissue biopsy is required. In cases of suspected amyloidosis with known organ impairment, the first diagnostic step is generally biopsy of the affected organ. In cases with no specific organ involvement, the first step is often a screening biopsy of the abdominal fat pad, rectal mucosa, or minor salivary glands. Abdominal fat pad biopsy, the preferred site, has a reported sensitivity of anywhere from 14 to over 90 percent, though this yield decreases substantially in patients with lower total body amyloid burdens.²

Once diagnosed, the prognosis of AL amyloidosis is highly variable depending on the organ systems affected. Historically the prognosis has been dismal, but recent advances in treatment and earlier detection...
rates have resulted in improved survival. Early detection therefore plays a critical role in maximizing outcomes. While nail changes are a relatively rare finding of systemic amyloidosis, they have been noted in at least 32 cases to date (Table 1).\textsuperscript{1,3-12} The nail changes most often described include increased brittleness, longitudinal ridging, and onycholysis, though chronic paronychia and verrucous subungual plaques have also been observed.\textsuperscript{1,10-11} Easy bruising, purpura, ecchymoses, and/or petechiae represent the most common cutaneous findings overall, present in 44 percent of the cases. Alopecia and macroglossia were the next most common mucocutaneous findings, seen in 39 percent and 23 percent of cases, respectively. Of note, 19 percent of the patients had a history of carpal tunnel syndrome, higher than its estimated prevalence in the general population.

Nail changes were the sole presenting sign of amyloidosis in almost 20 percent of the cases, highlighting its potential role in early detection. Moreover, in the 23 cases with a clear timeline, dystrophic nail changes began on average more than two and a half years prior to systemic presentation. In all cases where nail biopsy was undertaken, amyloid deposition was confirmed, indicating its promising diagnostic utility. Interestingly, one case even describes resolution of the nail dystrophy one year after autologous stem cell transplant, suggesting the possibility of reversibility with treatment.\textsuperscript{6}

In conclusion, we suggest a low threshold for consideration of nail bed biopsy in patients with trachyonychia, onychorrhexis, and onycholysis refractory to conventional treatment. This is particularly appropriate if other signs of systemic amyloidosis are present, for example macroglossia, alopecia, carpal tunnel syndrome, or known MGUS. Used in this manner, nail matrix biopsy may provide a reliable method for the early diagnosis of systemic amyloidosis, analogous to the current first-line diagnostic step of biopsy of an affected organ.

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