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LETTERS

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Relationship of radiographic progression to the pathogenic mechanism of rheumatoid arthritis: comment on the article by Molenaar et al

To the Editor:

The report by Molenaar and colleagues (1), as noted by Kirwan (2), does not fit the conventional concept of pathogenesis and therefore demands special scrutiny. Although osteoclasts are recognized as becoming activated in many conditions that are not inflammatory (e.g., in normal bone turnover), unbalanced turnover in osteoporosis and in metabolic bone diseases, the localized accumulation and activation of osteoclasts that produce the typical juxtaarticular erosions in rheumatoid arthritis (RA), has been considered to be determined by the localized production of cytokines by the inflammatory cells of the inflamed synovium. The report by Molenaar et al challenges this conventional model by their finding of new erosions in patients with RA judged by 2 different criteria to be in clinical remission. The authors mention that the criteria for clinical remission may not be sufficiently sensitive to rule out some degree of residual inflammation, and this seems to be a very likely possibility.

In my opinion, the continuation of the erosive process during periods when multiple examinations satisfy the American College of Rheumatology (3) and the disease activity score (4) criteria for remission is a strong argument that we need to carefully reexamine these criteria and consider how they could be modified to be more sensitive to limited, localized inflammation. Is an erythrocyte sedimentation rate of up to 33 mm/hour really normal? How reproducible are swollen joint counts in patients with minimal or no joint symptoms? How well would the swollen joint examinations agree with ultrasound or magnetic resonance imaging examination of the synovial swelling?

Kirwan has indulged in speculating on other possibilities for the continuing erosive process, but the model he proposed does not take into account that the synovial proliferation is most likely a response to the inflammatory process rather than an independent process. Although he considers the separation of cartilage loss and bone resorption to significantly support his proposed model, it has been known for some time that different mechanisms are responsible for these destructive effects that arise as a result of the inflammatory process, as well as examples of cartilage loss in the absence of inflammation or when inflammation is minimal (e.g., thinning of cartilage occurring in normal aging and osteoporosis).

Finally, the authors did not present any evidence on the magnitude of the "noise" in scoring radiographic damage in their series. It is well accepted that exact reproducibility of radiographic scores for both erosions and joint space narrowing is not seen with present-day methods of scoring films in RA. At the very least, a large subset of the images should have been read twice by each observer, and the limits of agreement and/or the smallest detectable difference should have been calculated and included in this report. The intraclass correlation between the scores of the 2 readers was impressively high, but this correlation coefficient does not tell us how much variation there might be in individual scores.

I commend the authors for conducting this study and raising this important question. The report is fascinating and very provocative and suggests a number of ways in which we can improve studies on radiographic progression and its relationship to the pathogenic mechanism of RA. It also brings front and center the urgent need to reexamine the criteria for remission in RA.

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1. Molenaar ET, Voskuyl AE, Dinant HJ, Bezemer PD, Boers M, Dijkmans BA. Progression of radiologic damage in patients with rheumatoid arthritis in clinical remission. Arthritis Rheum 2004;50:36–42.
2. Kirwan JR. The synovium in rheumatoid arthritis evidence for (at least) two pathologies. Arthritis Rheum 2004;50:1–4.
3. Pinals RS, Masi AT, Larsen RA, and the Subcommittee for Criteria of Remission in Rheumatoid Arthritis of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for clinical remission in rheumatoid arthritis. Arthritis Rheum 1981;24:1308–15.
4. Van der Heijde DM, van 't Hof MA, van Riel PL, Theunisse LM, Lubberts EW, van Leeuwen MA, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann Rheum Dis 1990;49:916–20.

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Radiologic progression and clinical remission in rheumatoid arthritis: comment on the article by Molenaar et al

To the Editor:

Molenaar and colleagues (Molenaar ET, Voskuyl AE, Dinant HJ, Bezemer PD, Boers M, Dijkmans BA. Progression of radiologic damage in patients with rheumatoid arthritis in clinical remission. Arthritis Rheum 2004;50:36–42) report that despite the presence of clinical remission in rheumatoid arthritis (RA), radiographs of the hands of RA patients showed progression of disease.

What needs to be emphasized is that the study also showed that controlling disease activity in rheumatoid patients is really an effective way to prevent progression of joint destruction (over 2 years, progression was observed in 7% of patients with persistent remission compared with 23% of patients with exacerbation). The authors agree that repeated observations are needed to recognize disease activity when it surfaces. Is assessment every 3 months enough? Would more frequent observation identify patients whose RA is not in remission?

In our 1971 study, we observed that 3 of 11 patients with inactive disease showed progression of erosions, compared with 16 of 46 patients with active disease (Karten I, O'Brien WM, Becker MH, McEwen C. Articular erosions in rheumatoid arthritis. J Chronic Dis 1972;25:449–56). We concluded that multiple measurements of disease activity by themselves are not sufficiently reliable to assess the long-term

course of RA. We agree with Molenaar et al that "structure is an important dimension of the concept of remission."

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Should the definition of clinical remission of rheumatoid arthritis be revised? Comment on the article by Molenaar et al

To the Editor:

Molenaar and colleagues make an important contribution to our understanding of the importance of controlling disease rather than just reducing its severity (Molenaar ET, Voskuyl AE, Dinant HJ, Bezemer PD, Boers M, Dijkmans BA. Progression of radiologic damage in patients with rheumatoid arthritis in clinical remission. Arthritis Rheum 2004;50:36–42). They suggest that rheumatoid arthritis (RA) can still produce erosions (as detected radiologically) even during clinical remission.

This suggestion is seemingly in conflict with other evidence (e.g., archeologic). As previously reported, the frequency of macroscopically detectable erosions in the skeletons of individuals with RA from archeologic sites was indistinguishable from the frequency of swelling/synovitis in contemporary clinical populations (Rothschild BM, Woods RJ. Synovitis equivalent to erosions in rheumatoid arthritis: implications of skeletal analysis for the clinical management of contemporary rheumatoid arthritis. Clin Exp Rheumatol 1992; 10:117–22). The 2 groups were comparable in composition, given their indistinguishable frequencies of radiologic findings. It was therefore suggested that any therapeutic intervention that settles for only partial control of synovitis would not prevent progression of erosive disease.

Because the study by Molenaar et al would appear to upset this paradigm, special scrutiny is required, especially as to the definition of clinical remission. The American College of Rheumatology criteria for clinical remission of RA (Pinals RS, Masi AT, Larsen RA, and the Subcommittee for Criteria of Remission in Rheumatoid Arthritis of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for clinical remission in rheumatoid arthritis. Arthritis Rheum 1981;24:1308–15) requires fulfillment of 5 of 6 criteria, only one of which relates to swelling. Thus, some individuals who fulfill the criteria will still have joint swelling. Only development of new erosions in individuals with sustained remission would support the contention that radiologic damage can progress in patients with RA in clinical remission.

In the study by Molenaar et al, examination of new lesion development in 14 patients revealed that only 2 were actually free of disease exacerbation during the study period. Although those 2 individuals fulfilled the criteria for sustained complete remission, it is critical to learn whether swelling was present at any time in the study interval.

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Reply

To the Editor:

We appreciate the interest shown in our recent study of the progression of radiologic damage in patients with RA in clinical remission. Dr. Sharp states that our report does not fit the conventional concept of the pathogenesis of inflammation and damage. In the conventional model, the inflammatory cells in the inflamed synovium produce cytokines that activate the osteoclasts that produce the typical erosions in RA. When applying the model to clinical studies, inflammation is generally reflected as swollen joint counts or acute-phase reactants. Minimal inflammation may be present to cause bone erosions, but such minimal inflammation may not be detected by clinical measures of disease activity.

We agree with the statement by Dr. Sharp that the current criteria for RA remission (1) need to be modified in order to detect inflammation more sensitively. For modification of the remission criteria, possibly other markers are needed, such as biochemical markers of bone metabolism or ultrasound or magnetic resonance imaging. However, these measures have to be evaluated first, and some are currently not easily performed in clinical studies. Whether inflammation would be monitored more accurately with such markers of inflammation or whether more frequent clinical assessment of arthritis activity, as suggested by Dr. Karten (2), is more appropriate is currently difficult to determine. Another point raised by Dr. Sharp is reproducibility of radiographic scores for erosions and joint space narrowing. To overcome the "noise" in scoring radiographic damage, the smallest detectable difference in progression scores for the same patients, as determined by the 2 observers, was calculated and appeared to be 5 (3). This was the reason for categorizing the patients described in our study into those with and those without relevant progression, using the cutoff of 5 points on the Sharp/van der Heijde index (4).

Furthermore, the smallest detectable difference for interobserver variability was calculated and found to be 3.6 for one observer (EM) and 3.5 for the other observer (HD). Finally, because the between-observer intraclass correlation coefficient (ICC) is invariably smaller than the within-observer ICC in reliability studies, we believe that we provided adequate information about the reliability of the readings in our study.

Dr. Rothschild's comment deals with the question of how many patients among those with new lesions were actually free of disease exacerbation. We would like to emphasize the findings in our study that a new erosion developed in a previously unaffected joint in 14 patients with RA in remission, of whom 11 were found to have no swollen joints during the 2-year followup period.

The finding in our study that joint damage can progress in patients with RA in remission is consistent with previous studies, as mentioned by Karten and Rothschild. We observed that radiologic progression occurs in patients classified "clinically" as being in remission. As a consequence, a concept of *complete* remission is proposed that should include both clinical and radiologic remission.

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1. Pinals RS, Masi AT, Larsen RA. Preliminary criteria for clinical remission in rheumatoid arthritis. Arthritis Rheum 1981;24: 1308–15.
2. Karten I, O'Brien WM, Becker MH, McEwen C. Articular erosions in rheumatoid arthritis. J Chronic Dis 1972;25:449–56.
3. Lassere M, van der Heijde D, Johnson K, Bruynesteyn K, Molenaar E, Boonen A, et al. Robustness and generalizability of smallest detectable difference in radiological progression. J Rheumatol 2000;28:911–3.
4. Van der Heijde DM, van Riel PL, Nuver-Zwart IH, Gribnau FW, van de Putte LB. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. Lancet 1989;1:1036–8.

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Life-threatening hypertriglyceridemia during leflunomide therapy in a patient with rheumatoid arthritis

To the Editor:

Leflunomide has been implicated in inducing hypercholesterolemia in patients with rheumatoid arthritis (RA) (Prokopowitsch AS, Diógenes AH, Borges TC, Torigoe D, Kochen J, Laurindo IM. Leflunomide induces progressive increase in rheumatoid arthritis lipid profile [abstract]. Arthritis Rheum 2002;46 Suppl 9:S164), but its effect on triglycerides is not well known. We report a case of life-threatening hypertriglyceridemia in a patient with RA treated with leflunomide.

The patient, a 60-year-old woman, was hospitalized because of hypodermitis (sclerosing panniculitis) of the lower limbs. RA was diagnosed in 1993, and the patient has been treated with leflunomide (20 mg/day) and prednisolone (5 mg/day) for the past 2 years. For several years, she has also been receiving diuretics (spironolactone [50 mg/day] and furosemide [20 mg/day]) and monoxidine (0.2 mg/day) for arterial hypertension, and atorvastatin (10 mg/day) for hypercholesterolemia.

At the time of admission, the patient's body mass index was 29. A rheumatologic examination did not reveal any inflamed joints. The lower limbs presented a hypodermal cyanotic pattern, while peripheral pulses were still present. Laboratory analysis revealed thrombocytopenia (platelet count 51,000/mm^3) without any other hematologic abnormalities, an erythrocyte sedimentation rate of 4 mm/hour, a C-reactive protein level of 22 mg/liter, glycemia (blood glucose level 1.2 gm/liter), hypercholesterolemia (blood cholesterol level 8.04 mg/dl [normal range 1.5–2.8 mg/dl]), and hypertriglyceridemia (blood triglyceride level 54.34 mg/dl [normal range 0.5–1.7 mg/dl]). Leflunomide was definitively discontinued, and a washout procedure was performed while introducing cholestyramine (8 gm three times daily for 11 days). To prevent myocardial infarction and pancreatic disorders, insulin therapy was immediately initiated. The triglyceride level rapidly decreased to 3 gm/liter, while the cholesterol level itself normalized.

It is relevant that the severe hypertriglyceridemia observed in our patient should be attributed to leflunomide therapy. While the patient was treated with atorvastatine, she was being monitored biologically, and no hypertriglyceridemia was noted. Thus, during leflunomide therapy, hypercholesterolemia developed (up to 3 mg/dl). The development of hypertriglyceridemia 24 months after the patient started leflunomide therapy represents the delay usually observed for this kind of metabolic abnormality. Prokopowitsch et al reported that in their study, triglyceride levels were increased only after 18 months of leflunomide treatment, while the level of low-density lipoprotein cholesterol began increasing after 6 months of treatment.

It is already known that hypercholesterolemia is a classic adverse effect observed during leflunomide treatment, but no severe case of hypertriglyceridemia has ever been reported. Our observation raises the question of a new and possibly severe adverse effect of leflunomide, which must be taken into account to prevent cardiovascular complications, because a recent Swedish study showed that RA patients presented an increased risk of cardiovascular complications related to their disease (Jarenros A, Jacobson LT, Turesson C. Increased incidence of myocardial infarction and stroke in rheumatoid arthritis: results from a community based study [abstract]. Arthritis Rheum 2002;46 Suppl 9:S510).

In conclusion, the lipid profile should be strictly monitored during the followup of RA patients treated with leflunomide to avoid complications of severe dyslipidemia, particularly hypertriglyceridemia.

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Large vessel compromise in antineutrophil cytoplasmic antibody–associated systemic vasculitis: comment on the article by Booth et al

To the Editor:

We read with interest the recent study by Booth et al (1), who report increased arterial stiffness as determined by the analysis of arterial waveforms by applanation tonometry and calculation of the aortic pulse wave velocity in patients with antineutrophil cytoplasmic antibody (ANCA)–associated systemic vasculitis (AASV). Their report is consistent with previous studies in rheumatoid arthritis (RA) (2,3), which have suggested that systemic inflammation may result in changes in arterial stiffness. Regarding previous studies in end-stage renal disease (ESRD) and RA (2–4), Booth et al correctly point out that "direct involvement of the large arteries in the disease

process in these two conditions may account for any observed changes in arterial stiffness, rather than systemic inflammation per se." They also state that this is one of the reasons that prompted them to study patients with AASV and to propose AASV as a model of systemic inflammation for evaluating therapies that improve systemic vascular health and reduce cardiovascular risk.

However, the authors did not consider large vessel compromise, which does occur in ANCA–associated small vessel vasculitis (5), as a potential confounder. When clinically manifest, large vessel vasculitis in AASV can present as luminal stenosis, arterial dilation, perivascular masses, or arterial dissection (5). Although manifest large vessel compromise in AASV is rare, the frequency of subclinical large vessel disease in AASV is unknown. It has been reported that labeled leukocyte or fluorodeoxyglucose isotopic studies can reveal otherwise unsuspected large vessel compromise in patients with AASV (5,6). In the original report of 3 cases of Wegener's granulomatosis (WG), histologic evidence of (subclinical) large vessel vasculitis occurred in 1 case. Large vessel (peri)vascular involvement has also been seen in a more recent series of patients with WG (7). The frequency of subclinical large vessel involvement in AASV, however, has not been specifically studied. Therefore, it is possible that subclinical large vessel compromise in these patients may confound determinations of arterial stiffness in the very same way Booth et al propose for RA and ESRD.

We believe that until these issues are clarified or subclinical large vessel compromise is specifically evaluated in clinical studies of arterial stiffness, ANCA-associated small vessel vasculitis should not be considered an optimal model for assessing systemic inflammation and its relationship to large vessel arterial stiffness.

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1. Booth AD, Wallace S, McEniery CM, Yasmin, Brown J, Jayne DR, et al. Inflammation and arterial stiffness in systemic vasculitis: a model of vascular inflammation. Arthritis Rheum 2004;50:581–8.
2. Wong M, Toh L, Wilson A, Rowley K, Karschimkus C, Prior D, et al. Reduced arterial elasticity in rheumatoid arthritis and the relationship to vascular disease risk factors and inflammation. Arthritis Rheum 2003;48:81–9.
3. Klocke R, Cockcroft JR, Taylor GJ, Hall IR, Blake DR. Arterial stiffness and central blood pressure, as determined by analysis, in rheumatoid arthritis. Ann Rheum Dis 2003;62:414–8.
4. Blacher J, Safar ME, Guerin AP, Pannier B, Marchais SJ, London GM. Aortic velocity index and mortality in end-stage renal disease. Kidney Int 2003;63:1852–60.
5. Chirinos JA, Tamariz LJ, Lopes G, Del Carpio F, Zhang X, Milikowski C, et al. Large vessel involvement in ANCA-associated vasculitides: report of a case and review of the literature. Clin Rheumatol 2004;23:152–9.
6. Fink AM, Miles KA, Wraight EP. Indium-111 labelled leukocyte uptake in aortitis. Clin Radiol 1994;49:863–6.
7. George TM, Cash JM, Farver C, Sneller M, van Dyke CW, Derus CL, et al. Mediastinal mass and hilar adenopathy: rare thoracic manifestations of Wegener's granulomatosis. Arthritis Rheum 1997;40:1992–7.

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Reply

To the Editor:

Dr. Chirinos and colleagues suggest that subclinical large vessel involvement in AASV is a potential confounding factor in our study, demonstrating a link between inflammation and aortic stiffness. In support of his argument, he cites a case report of clinically significant large vessel involvement in microscopic polyangiitis. Nonetheless, reports of symptomatic large vessel involvement in AASV are rare.

The true prevalence of subclinical large vessel involvement in AASV, based on histologic analysis, remains uncertain. However, a variety of techniques such as imaging with indium-111, gallium-67, or 18-fluorodeoxyglucose, and both ultrasonography and computed tomography scanning, have been used to assess this important question noninvasively. Indium white cell scanning in patients with AASV has been extensively performed in our own and one other center, with no evidence of aortic uptake demonstrated (1,2). Moreover, Chirinos et al cite a retrospective series of 1,100 patients with unexplained fever in whom only one patient with WG had increased uptake in the aorta (3). Although one case of periaortitis in a patient with WG has been described using fluorodeoxyglucose–positron emission tomography scanning, this may have been attributable to involvement of the vasa vasorum (4). The other potential explanation for the isolated case reports of large vessel involvement in ANCA-associated vasculitis is either disease misclassification or disease overlap with larger vessel vasculitides such as Takayasu arteritis and polyarteritis nodosa (5,6).

Both systemic inflammation and arterial stiffness predict cardiovascular risk in persons with, and at risk of, cardiovascular disease, and we used AASV as a model of inflammation to demonstrate a link between the 2 risk factors. Interestingly, AASV would appear to be, itself, associated with increased cardiovascular risk. Nevertheless, it remains unclear whether the circulating inflammatory mediators associated with organ disease alter functional activity of the large vessels, or whether there is indeed direct inflammatory infiltration of the large vessels. Although we accept that direct involvement of the aorta has rarely been reported in AASV, we do not believe that this is likely to represent a significant confounding factor in our study, particularly because we specifically excluded patients with clinical evidence of vascular disease affecting the coronary, carotid, or peripheral vascular territories.

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1. Reuter H, Wraight EP, Qasim FJ, Lockwood CM. Management of systemic vasculitis: contribution of scintigraphic imaging to evaluation of disease activity and classification. Q J Med 1995;88:509–16.
2. Jonker ND, Peters AM, Gaskin G, Pusey CD, Lavender JP. A

retrospective study of radiolabeled granulocyte kinetics in patients with systemic vasculitis. J Nucl Med 1992;33:491–7.
3. Fink AM, Miles KA, Wraight EP. Indium-111 labelled leucocyte uptake in aortitis. Clin Radiol 1994;49:863–6.
4. Blockmans D. The use of (18F)fluoro-deoxyglucose positron emission tomography in the assessment of large vessel vasculitis. Clin Exp Rheumatol 2003;21(6 Suppl 32):S15–22.
5. Nakabayashi K, Kamiya Y, Nagasawa T. Aortitis syndrome associated with positive perinuclear antineutrophil cytoplasmic antibody: report of three cases. Int J Cardiol 2000;75 Suppl 1:S89–94.
6. Yamasaki S, Eguchi K, Kawabe Y, Tsukada T, Nagataki S. Wegener's granulomatosis overlapped with Takayasu arteritis. Clin Rheumatol 1996;15:303–6.

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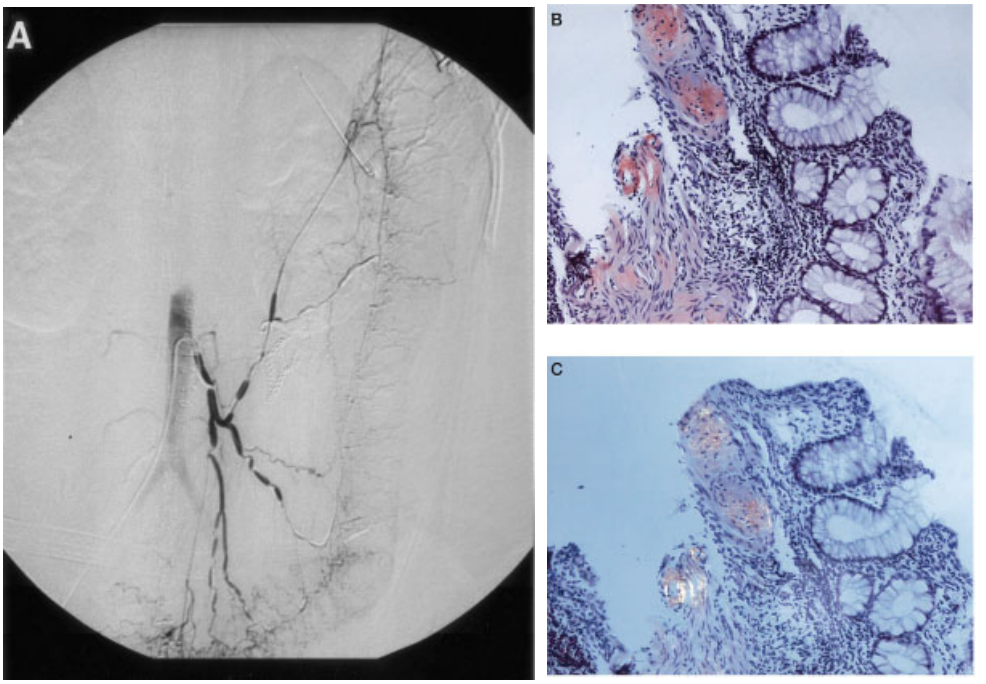
Clinical Images: Primary systemic amyloidosis masquerading as necrotizing vasculitis



The patient, a previously healthy woman, developed a small bowel perforation. Surgical examination revealed extensive bowel thickening with diffuse segmental ischemia. Physical examination results were normal except for periorbital ecchymosis, dystrophic nails, and a purpuric rash. Findings on visceral angiography were strongly suggestive of necrotizing vasculitis in all vascular beds, with segmental arterial strictures and fusiform aneurysms as illustrated in the inferior mesenteric artery (**A**). However, on pathologic examination of the bowel, there was no evidence of vasculitis, whereas significant amyloid deposition was revealed (**B**) (Congo red stain). Characteristic apple-green birefringence on polarized microscopy confirmed the presence of amyloid (**C**). Serum immunofixation revealed an M-spike of monoclonal lambda protein. The patient's condition improved remarkably with thalidomide treatment and total parenteral nutrition, with resolution of the M-spike. In a patient with features of vasculitis but negative biopsy results for this disease, the possibility of primary systemic amyloidosis should be considered. Primary amyloidosis can mimic vasculitides, especially giant cell (temporal) arteritis or polymyalgia rheumatica (1–3). Rarely, it can coexist with necrotizing vasculitis of the central nervous system, giant cell arteritis, or vasculitis of the small intestine (1,4,5).

1. Salvarani C, Gabriel SE, Gertz MA, Bjornsson J, LI CY, Hunder GG. Primary systemic amyloidosis presenting as giant cell arteritis and polymyalgia rheumatica. Arthritis Rheum 1994;37:1621–6.
2. Ing EB, Woolf IZ, Younge, BR, Bjornsson J, Leavitt JA. Systemic amyloidosis with temporal artery involvement mimicking temporal vasculitis. Ophthalmic Surg Lasers Imaging 1997;28:328–31.
3. Rao JK, Allen NB. Primary systemic amyloidosis masquerading as giant cell arteritis: case report and review of the literature. Arthritis Rheum 1993;36: 422–5.
4. Oweity T, West AB, Stokes MB. Necrotizing angiitis of the small intestine related to AA-amyloidosis: a novel association. Int J Surg Pathol 2001;9:149–54.
5. Le Coz P, Mikol J, Ferrand J, Woimant F, Masters C, Beyreuther K, et al. Granulomatous angiitis and cerebral amyloid angiopathy presenting as mass lesion. Neuropathol Appl Neurobiol 1991;17:149–55.

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