

Etanercept-Related Extensive Pulmonary Nodulosis in a Patient with Rheumatoid Arthritis

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ABSTRACT. Although nodulosis is a common extraarticular manifestation of rheumatoid arthritis, accelerated pulmonary nodulosis is a rare event. The etiology of rheumatoid nodules is still unknown. Nodulosis is not necessarily associated with active joint inflammation, suggesting different pathogenic mechanisms for nodule formation and synovial tissue inflammation. We describe a patient with extensive pulmonary nodulosis, probably related to etanercept treatment. Our case emphasizes the need for careful monitoring for adverse events during treatment with biologicals, especially since the differential diagnosis often includes a broad spectrum of diseases. (First Release June 15 2007; *J Rheumatol* 2007;34:1590–2)

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NODULOSIS
ETANERCEPT

RHEUMATOID ARTHRITIS
ANTI-TUMOR NECROSIS FACTOR

Rheumatoid nodules occur in about 25% of patients with rheumatoid arthritis (RA)¹. Nodules are commonly located subcutaneously over sites of local pressure, but may also be found in lungs, heart, liver, eyes, dura, and bladder, and may cause complications. We describe a patient with accelerated pulmonary nodulosis.

CASE REPORT

A 50-year-old man attended the outpatient clinic because of a painful left shoulder. He had a 10-year history of seropositive erosive RA. During the last 12 months he developed subcutaneous nodules over both arms. In the past he was treated with methotrexate (lack of efficacy), sulfasalazine (adverse events), and infliximab (infusion reaction). On presentation he was on a regimen of leflunomide (20 mg/day for 3 yrs) and etanercept (25 mg twice weekly for 2 yrs).

Clinical examination showed arthritis of the left shoulder. Shoulder radiographs showed minor bony erosions. In addition, multiple densities were observed in the apical part of the left lung. Chest radiography and high resolution computed tomography revealed disseminated bilateral, partly confluating nodules, some pleural thickening, and pleural effusion (Figure 1A, 1B). A restrictive pulmonary function test was observed (total lung capacity 4.21 l, normal 6.42 l). Bronchoscopy and bronchoalveolar lavage revealed no abnormalities. Thoracoscopy and minithoracotomy were performed to obtain pleural and lung biopsies of multiple nodules. Histological examination showed no infection, malignancy, or vasculitis, but typical features of rheumatoid nodules (palisading histiocytic and chronic inflammatory cells, arrayed about an area of central fibrinoid necrosis). In addition, some lymphoplasmocytic

infiltrate and fibrosis were seen. All cultures, including *Mycobacterium*, were negative.

Because of the extent of the pulmonary nodules and case reports of serious and sometimes lethal complications, in addition to the time relationship with the drug treatment, both leflunomide and etanercept were discontinued and treatment with prednisone (40 mg/day) and azathioprine (2.5 mg/kg/day) was initiated. Three months later, both pulmonary and subcutaneous nodules had largely disappeared (Figure 1C). During followup no recurrence of nodules was seen and the lung status remained stable.

DISCUSSION

Nodulosis is the most frequent extraarticular manifestation in RA¹. Preferentially, nodules are located subcutaneously, but the frequency of nonperipheral nodules is probably underestimated. There are several predisposing factors, such as a positive rheumatoid factor, severe articular disease, smoking, and genetic predisposition (HLA-DRB1). However, the pathogenesis of rheumatoid nodules is still unknown.

Histopathologically, a rheumatoid nodule is a dynamic granuloma: a necrotic center surrounded by palisading macrophages and fibroblasts, and an outer layer consisting of perivascular infiltrating mononuclear cells¹. Some evidence supports a role for immune complexes, subsequent complement activation, and vasculitis, resulting in granuloma formation². Clinically, patients with RA may develop nodules irrespective of low disease activity, suggesting that different pathogenic mechanisms mediate nodule formation and synovial tissue inflammation³. In addition, histologic characteristics, expression of adhesion molecules, and cytokine profiles show both similarities and differences between rheumatoid nodules and inflamed synovial tissue^{4–6}.

Generally, pulmonary rheumatoid nodulosis is characterized by asymptomatic and stable, solitary, or small numbers of nodules. Rarely, however, these pulmonary nodules may cause considerable morbidity and even mortality⁷. The Caplan

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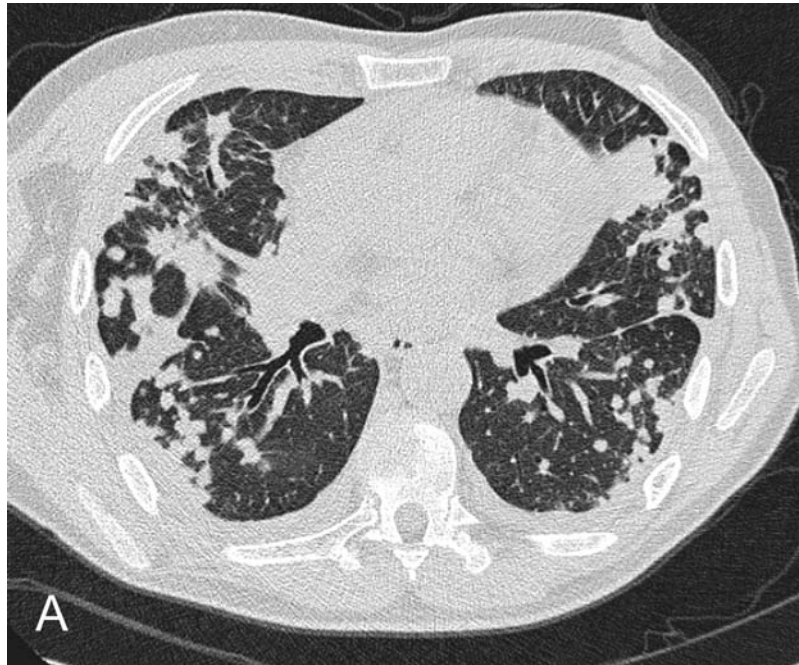


Figure 1. High resolution CT scanning (A) and plain chest radiographs (B, C) of the lungs before (A, B) and after (C) withdrawal of etanercept treatment and start of prednisone and azathioprine. Extensive symmetrical pulmonary nodulosis is seen predominantly in the lower lungs, together with pleural thickening, slight pleural effusion, and moderate mediastinal lymphadenopathy. After 3 months, clear regression of the majority of noduli can be seen.

syndrome is a distinct clinical entity encompassing the development of pulmonary rheumatoid nodules in patients exposed to silica dust. This syndrome is characterized by large nodules in the upper lung lobes and clearly differs from the numerous small nodules seen in our patient⁸.

In our patient, nodulosis is probably related to concomitant etanercept treatment. Although for obvious reasons a challenge was not performed, several arguments favor this hypothesis: (1) our patient had longstanding RA without developing rheumatoid nodules prior to treatment with etanercept; (2) pulmonary nodulosis was unusually extensive; (3)

disease activity was low; (4) after withdrawal of etanercept and leflunomide the nodulosis subsided very quickly; (5) since leflunomide has a very long half-life and no washout procedure was performed, it seems unlikely that the discontinuation of leflunomide could result in such a rapid improvement; (6) extensive investigation, including multiple lung biopsies, showed no other disease entities.

Accelerated nodulosis is a well recognized complication of methotrexate treatment⁹. Five patients have been reported who developed subcutaneous or pulmonary nodules during treatment with leflunomide^{10,11}. However, no cases with dis-

Table 1. Reported cases of leflunomide or biological-induced nodulosis in RA.

	Sex, age, RF	Pre-existent Nodules	New Nodules	Time to Event (mo)	Drug Withdrawal	Treatment	Outcome
Etanercept							
1	M, 52, +	SC	SC	2	No	Lef	Stable
2	M, 50, +	SC	SC	3	No	Lef	Stable
3	M, 67, +	No	Lungs, multiple, large	2	Yes	Pred/Aza	Regression < 3 mos
4	F, 53, +	SC	Lungs/SC, multiple	4	Yes	No	Regression < 2 mos
5	F, 41, +	SC	Lung, multiple	21	Yes	No	?
Present case	M, 50, +	No	Lungs/SC, multiple, small	12	Yes	Pred/Aza	Regression < 3 mos
Infliximab	None						
Adalimumab	None						
Anakinra	None						
Leflunomide							
1	M, 77, +	SC	Lungs, multiple	13	Yes	No	Stable
2	M, 66, +	SC	Lungs, multiple	7	Yes	No	Stable
3	F, 38, +	No	SC	6	No	No	?
4	F, 66, +	SC	SC	6	Yes	No	?
5	M, 67, +	No	SC	6	Yes	No	?

RF: rheumatoid factor; SC: subcutaneous; Lef: leflunomide; Pred: prednisone; Aza: azathioprine.

seminated pulmonary nodulosis were included. Although small clinical trials and histopathological studies with tumor necrosis factor (TNF) blockade (infliximab and etanercept) have shown neither a beneficial effect on nodulosis nor its acceleration^{5,12}, 5 cases of etanercept-associated subcutaneous or pulmonary nodulosis have been published^{4,13,14} (Table 1). Our case is distinguished by the extensiveness of the pulmonary nodulosis.

The pathogenic mechanism of drug-induced nodulosis is unknown. For methotrexate a role for adenosine has been suggested. More recently, apoptosis as an important regulator of the dynamics of a granuloma was proposed. Rheumatoid nodules show low levels of apoptosis and small numbers of apoptotic cells, compared with sarcoid granulomas¹⁵. In contrast to use of etanercept, accelerated nodulosis has not been reported for infliximab or adalimumab. This might be due to differences in their potential for binding membrane-bound TNF and subsequent apoptosis. The same mechanism might also account for differences in efficacy of treatment of granulomatous diseases and the occurrence of tuberculosis.

The differential diagnosis of pulmonary nodulosis is extensive, including malignancies (lymphangitis carcinomatosa, broncho-alveolar-cell carcinoma), (opportunistic) infections (tuberculosis, histoplasmosis, coccidioidomycosis), toxic (silicosis), and idiopathic causes (sarcoidosis, amyloidosis, histiocytosis). This case shows that etanercept treatment in RA can be associated with extensive (pulmonary) nodulosis and emphasizes the need for careful monitoring during treatment with biologicals.

REFERENCES

- Ziff M. The rheumatoid nodule. *Arthritis Rheum* 1990;33:761-7.
- Kato H, Yamakawa M, Ogino T. Complement mediated vascular endothelial injury in rheumatoid nodules: a histopathological and immunohistochemical study. *J Rheumatol* 2000;27:1839-47.
- Baeten D, De Keyser F, Veys EM, Theate Y, Houssiau FA, Durez P. Tumour necrosis factor alpha independent disease mechanisms in rheumatoid arthritis: a histopathological study on the effect of infliximab on rheumatoid nodules. *Ann Rheum Dis* 2004;63:489-93.
- Cunnane G, Warnock M, Fye KH, Daikh DI. Accelerated nodulosis and vasculitis following etanercept therapy for rheumatoid arthritis. *Arthritis Rheum* 2002;47:445-9.
- Elewaut D, De Keyser F, De Wever N, et al. A comparative phenotypical analysis of rheumatoid nodules and rheumatoid synovium with special reference to adhesion molecules and activation markers. *Ann Rheum Dis* 1998;57:480-6.
- Wikanangrum R, Highton J, Parker A, et al. Pathogenic mechanisms in the rheumatoid nodule: comparison of proinflammatory cytokine production and cell adhesion molecule expression in rheumatoid nodules and synovial membranes from the same patient. *Arthritis Rheum* 1998;41:1783-97.
- Kitamura A, Matsuno T, Narita M, Shimokata K, Yamashita Y, Mori N. Rheumatoid arthritis with diffuse pulmonary rheumatoid nodules. *Pathol Int* 2004;54:798-802.
- Arakawa H, Honma K, Shida H, Saito Y, Morikubo H. Computed tomography findings of Caplan syndrome. *J Comput Assist Tomogr* 2003;27:758-60.
- Patatanian E, Thompson DF. A review of methotrexate-induced accelerated nodulosis. *Pharmacotherapy* 2002;22:1157-62.
- Braun MG, Van Rhee R, Becker-Capeller D. Development and/or increase of rheumatoid nodules in RA patients following leflunomide therapy. *Z Rheumatol* 2004;63:84-7.
- Rozin A, Yigla M, Guralnik L, et al. Rheumatoid lung nodulosis and osteopathy associated with leflunomide therapy. *Clin Rheumatol* 2005;7:1-5.
- Kaiser MJ, Bozonnat MC, Jorgensen C, Daures JP, Sany J. Effect of etanercept on tenosynovitis and nodules in rheumatoid arthritis. *Arthritis Rheum* 2002;46:559-60.
- Kekow J, Welte T, Kellner U, Pap T. Development of rheumatoid nodules during anti-tumor necrosis factor alpha therapy with etanercept. *Arthritis Rheum* 2002;46:843-4.
- Hubscher O, Re R, Iotti R. Pulmonary rheumatoid nodules in an etanercept-treated patient. *Arthritis Rheum* 2003;48:2077-8.
- Highton J, Hessian PA, Kean A, Chin M. Cell death is a feature of the rheumatoid nodule. *Ann Rheum Dis* 2003;62:77-80.