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Are rheumatoid nodules caused by vasculitis? A study of 13 early cases

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SUMMARY Rheumatoid nodules are especially found in patients with seropositive rheumatoid arthritis (RA). It is often suggested that the genesis of these lesions is due to a vasculitis in smaller capillary vessels or venules. To test this hypothesis we studied fresh nodules in 13 patients, all with classical or definite RA. In 7 cases a total of 8 nodules were removed within 10 days of origin and in 6 other cases between 2 and 8 weeks. In the former group immunofluorescence was found in 5 out of 8 cases, and in the latter group 3 out of 6 were positive. Immunoglobulin deposition together with complement was found only in cases of 10 days' duration or less. No correlation was found with the patient's age or disease duration, ESR, ANA positivity, Rose titre, haemoglobulin, or use of prednisolone. In 3 out of 7 nodules younger than 7 days no palisade layer was found, whereas in older nodules this layer was always present. Vasculitis was not more frequently present in the cases with younger nodules. Our study does not support the hypothesis that vasculitis is the primary cause of nodules.

In many patients with rheumatoid arthritis (RA) rheumatoid nodules are found on pressure points at bony prominences like the olecranon. Despite many theories the pathogenesis of these nodules remains obscure. Nodules are especially found in patients with seropositive RA, and it has been speculated that these lesions might be caused by the local deposition of immune complexes. However, arteritis in large vessels is seldom seen in the neighbourhood of nodules, and so it was suggested that their genesis is due to a vasculitis in smaller capillary vessels or venules.[1-3] If this were true, one might expect that vasculitis and possibly immune complex deposition would be found in or near early rheumatoid nodules. To our knowledge a systematic investigation of these possibilities in early rheumatoid nodules has never been performed. By studying the pathological and immunofluorescent findings in early nodules, we hoped to shed some light on these questions.

Patients and methods

All patients who developed a 'fresh' rheumatoid nodule during their stay in hospital between 1977 and 1980 were asked to have this nodule removed. In all very early cases the exact day of origin could be defined. In older cases (more than 2 weeks) this was possible within a range of some days or a week, otherwise the patients were not included in this study. All nodules in this series were located around the elbow. The patients consisted of 6 females and 7 males. In one of these males 2 fresh nodules developed within a 2-week interval and were both removed. The mean age of the patients was 60·3 years and the mean duration of RA 8·6 years. One patient had definite and all the others classical RA. The characteristics of the patients are summarised in Table 1.

Immediately after excision the nodule was divided in 2 parts. One portion was fixed in 4% neutral formalin for routine histological examination. The other was embedded in gelatin and quickly frozen in liquid nitrogen in an aluminium box. Cryostat sections were used for direct and indirect immunofluorescence of IgA, IgM, IgG, complement C3, and fibrin. For controls normal rabbit serum was used. The sera were obtained from the Centraal Laboratorium Bloedtransfusiedienst, Amsterdam, and from Sanbio BV.

Results

In very fresh nodules (10 days or less) immunofluorescence was found in 5 out of 8 cases (Figs 1A

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Table 1 *Characteristics of patients from whom nodules were excised*

Patient no.	*Age*	*Sex*	*RF titre*	*Duration of disease (years)*	*Age of nodule*	*Medication*
1	60	M	neg.	1	3 days	Pred +D-pen
2	62	F	1:128	17	<7 days	Gold
3a	65	M	1:512	3	<7 days	D-pen
3b					<7 days	D-pen
4	57	F	1:512	18	<7 days	Cytotox
5	61	F	1:256	14	<7 days	Predn
6	55	F	1: 64	2	7 days	Antimalarials
7	58	M	1:128	12	10 days	Gold
8	47	M	1:128	6	2 weeks	Predn+D-pen
9	68	M	1:256	3	17 days	Antimalarials
10	50	M	1:128	5	4–5 weeks	Predn
11	61	F	1:128	14	5 weeks	Antimalarials
12	66	F	1:128	15	6 weeks	D-pen
13	60	M	1:128	1	8 weeks	—

D-pen = D-penicillamine. Cytotox = cytotoxic drugs. Predn = prednisone.

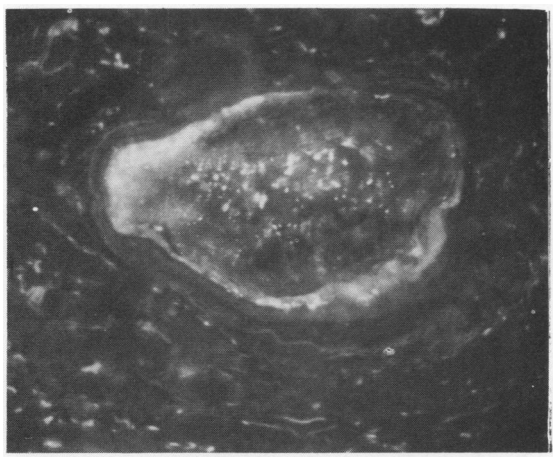

Fig. 1A *Immunofluorescence of IgM in vessel walls near early rheumatoid nodule. Case 3a.* (×300).

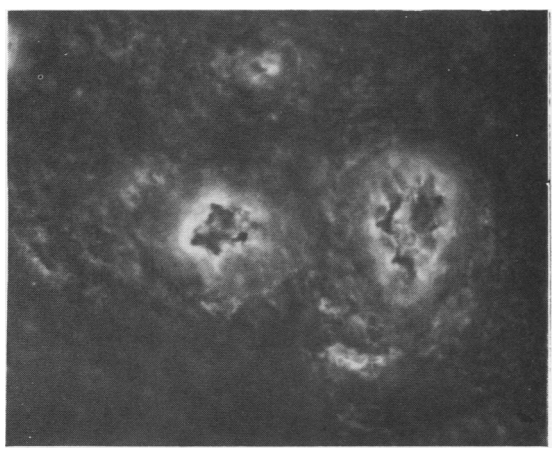

Fig. 1B *Immunofluoresence of IgG in vessel walls near early rheumatoid nodule. Case 3a.* (×300).

and B), in nodules of older age (2–8 weeks) 3 out of 6 were positive; in 5 cases the distribution was in or near the vessel wall and in 3 cases diffuse. Immunoglobulins together with complement were found only in cases of 10 days' duration or less (Table 2). No correlation was found with the patient's age or disease duration, erythrocyte sedimentation rate (ESR), antinuclear antibody (ANA) positivity, Rose titre, or haemoglobulin level.

Of the 8 cases with immunofluorescence 2 were female and 6 males. Prednisone or prednisolone was taken by 4 patients, 2 of them with positive immunofluorescence.

In 3 out of 7 nodules younger than 7 days no palisade layer was found, whereas in older nodules

Table 2 *Immunofluorescent findings (immunglobulin and C3 deposition) in early nodules (10 days old or less) and in late nodules (more than 2 weeks old)*

Patient no.	*Age of nodule*	*Immunofluorescence*
Early nodules		
1	3 days	IgM + C3 Vessel
2	<7 days	Negative
3a	<7 days	IgG + C3 Vessel
3b	<7 days	IgG + C3 Vessel
4	<7 days	Negative
5	<7 days	Negative
6	7 days	IgM Diffuse
7	10 days	IgM C3 Diffuse
Late nodules		
8	2 weeks	IgM Diffuse
9	17 days	Negative
10	4–5 weeks	Negative
11	5 weeks	IgM Vessel
12	6 weeks	Negative
13	8 weeks	C3 in Vessels

this layer was always present (Figs 2 and 3). There was no clear difference in any other respect between cases with younger and older nodules; in particular, vasculitis (cellular infiltration of walls of arterioles with or without thrombosis) was not more frequently present in younger cases (Table 3).

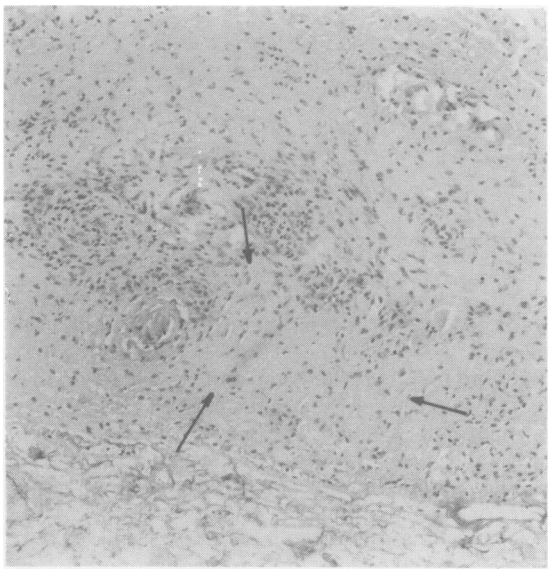

Fig. 2 *Early nodule with necrosis (arrows) without palisade layer. There is vasculitis. Case 3. (Haematoxylin-eosin, ×90).*

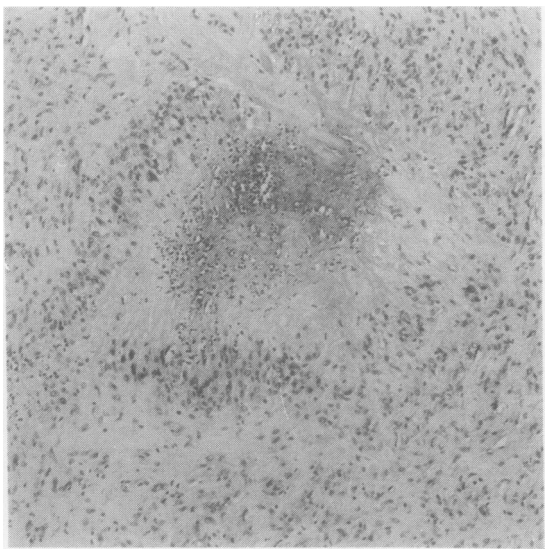

Fig. 3 *Older nodule with palisade layer around necrosis. Case 13. (×90).*

Table 3 *Pathological findings in patients with early modules (10 days or less) and in late nodulues (more than 2 weeks old)*

Patients no.	*Fibrinoid necrosis (degeneration)*	*Palisade of cells*	*Cavity formation*	*Histiocytes*	*Leucocytes*	*Lymphocytes*	*Plasma cells*	*Giant cells*	*Vascular granul. tissue*	*Fibrosis*	*Vasculitis*
Early nodules											
1	+	+	−	−	−	+	±	−	+	+	±
2	+	−	+	−	+	−	+	−	+	−	−
3a	+	−	−	+	−	+	+	−	+	+	+
3b	+	+	+	+	−	+	−	±	+	+	−
4	+	+	+	−	+	+	±	−	+	+	−
5	+	−	−	−	+	−	±	−	+	−	±
6	+	+	−	−	−	+	±	−	+	+	−
7	+	+	+	±	−	±	−	−	+	+	±
Late nodules											
8	+	±	−	+	−	−	±	−	+	−	−
9	+	+	+	−	−	+	+	−	+	+	−
10	+	+	+	−	−	+	+	−	+	+	−
11	+	+	−	−	+	±	±	−	+	+	+
12	+	+	+	−	−	−	±	−	+	+	−
13	+	+	+	±	−	±	−	−	+	+	+

There were no complications after excision of the nodules, no post operative infections or exacerbations of rheumatoid arthritis.

Discussion

The most remarkable finding here is that in most of these cases of early rheumatoid nodules no signs of vasculitis were found. Immunofluorescence was not found more frequently in early than in later cases, but immunoglobulins together with complement were found only in cases with nodules 10 days or younger. The presence of complement and Ig might have been an initiating mechanism for vasculitic lesions. In adult RA patients nodules are characterised by a central necrotic area, a palisade layer of macrophage or fibroblast-derived cells surrounding it. These surrounding cells are of macrophage nature, proliferate, and undergo successive waves of necrosis internally, so contributing to the necrotic centre; this consists entirely of cellular organelles and fibrin, with residual collagen fibres traversing it.[3 4] Sokoloff and Bunim[5] observed the palisade layer in the rheumatoid nodule on the 9th day, but not on the 7th day. Bennett *et al.*[6] on the contrary found a palisade layer in 7 rheumatoid nodules from several days onwards. In our series in 3 out of 7 cases younger than one week no palisade layer was found.

Fukasa *et al.*[7] microscopically classified a series of 16 nodules histologically for age. Though clinical age was unknown, they found immunofluorescence deposition more frequently in the supposedly earlier nodules than in the older group. As can be seen in Table 3, we could not confirm a relationship between clinical age of the nodule and the 'pathological age' as suggested by Fukasa, nor did we find immunoglobulin deposits more frequently in the earlier nodules. From our results it becomes clear that it is not possible to estimate the age of a nodule from morphological findings. The fact that immunoglobulins together with complement were found more frequently in nodules that were 10 days or younger could well fit with the idea that immune complex depsoition took place near the nodule. We did not find an association of the nodule with development within synovial lining of a bursa, as Ahern *et al.*[8] found. Ahern *et al.* found no clinical markers for vasculitis in patients with rheumatoid nodules, except perhaps a slightly increased serum IgG rheumatoid factor, even on rectal biopsy in only 1 out of 40 patients vasculitis was seen.

If immune complex deposition is the initial event in the life of a nodule, it is possible that in some cases the complex may have disappeared by the time the nodule has developed. But one would have still expected to find at least some evidence of vasculitis, especially in or near *all* the very early nodules. We could not confirm that microinfarction resulting from thrombosis of terminal vessels plays a role in necrosis formation as Harris[9] stated. Possibly the enormous quantities of proteinases and collagenases produced by the cellular palisading area play a major role.[9] Our study gives no support to the myth that taking out RA nodules may be dangerous, as no complications were seen.

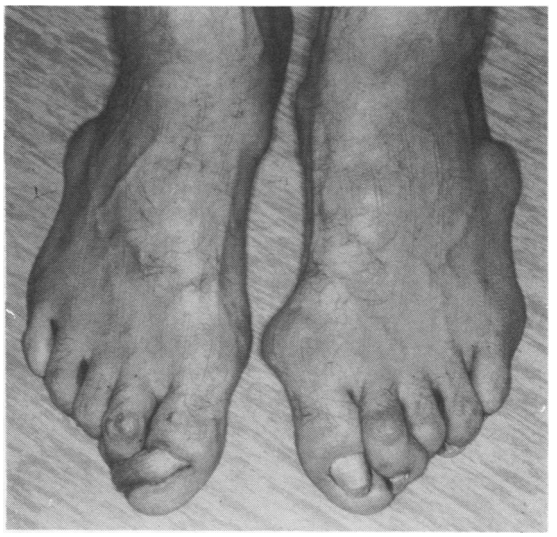

Fig. 4 *Rheumatoid nodules on the feet of a Dutch farmer, who wears wooden clogs.*

We could not confirm the findings of several other studies, neither could we give an explanation for the question why nodules come and sometimes go. Rheumatoid patients develop nodules on pressure points such as the elbows, sacral region, fingers etc. One typically Dutch localisation for nodules is pressure points on the feet due to wearing wooden shoes (Fig. 4). The only thing that remains clear is that local shearing stress plays a role in the development of nodules, but the exact genesis of nodules remains obscure.

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Book review

Hyperuricaemia and Gout in Clinical Practice. Ed. B. T. Emmerson. Pp. 159. £10·95. John Wright: Bristol. 1983.

This attractively and well produced book from Queensland, Australia, gives a very good résumé of what is known on the subject. The first 30 pages deal with the production and elimination of urate and uric acid and enzymatic and genetic factors. The criterion for hyperuricaemia is 7 mg/dl (0·42 mmol) in men and 6 mg/dl (0·36 mmol) in women. Its causes are well covered, as are its effects on attacks of gout, formation of calculi, hypertension, and renal disease. Their association figures are given, but the conclusion is that, except when there is already renal disease, hyperuricaemia, unless very high, is not a great risk. This conclusion may be contentious, but controlled trials back up this view. Hypertriglyceridaemia, alcohol consumption, and, surprisingly in these days, lead are associated factors. Overproduction occurs in only 16% of cases.

The clinical description of types of gout is good, as is the section on treatment. Colchicine mainly acts by inhibiting the crystal-released chemotactic factor, thus breaking the inflammatory cycle. The synopsis of the mode of action, absorption, and excretion of the nonsteroidal anti-inflammatory drugs is good, and the author deals with the uricosurics and xanthine oxidase inhibitors, believing the former group still has a great value for the many under-secretors. A thoughful section is included on the treatment of chronic complicated gout. The author shows his clinical acumen in his assessment of the doctor-patient relationship and the importance of the patient's understanding of the situation during remission. He believes that, even in these days of potent drug therapy, external factors contributing to the production of gout should not be forgotten. This small book is a worthwhile addition to the voluminous literature on the subject.

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