SUBCUTANEOUS NODULES OF STILL’S DISEASE*

BY

E. G. L. BYWATERS, L. E. GLYNN, AND A. ZELDIS†

From the Rheumatism Research Unit, Medical Research Council, Canadian Red Cross Memorial Hospital, Taplow, and the Postgraduate Medical School, London

The observations of Collins (1937) and of Bennett, Zeller, and Bauer (1940) established clearly the pathological differentiation of the ordinary subcutaneous nodules in rheumatic fever and in rheumatoid arthritis.

In brief, the rheumatic fever nodule is characterized by much fibrinoid material arranged in a lattice with apparently clear spaces between the strands, considerable oedema, but relatively little cellularity. What cells are present are usually fibroblasts or histiocytes; they are sparsely distributed in the meshes of oedematous connective tissue and accompanied occasionally by lymphocytes or rarely by polymorphs near the vascular “islands” (Fig. 1, opposite). There is little attempt at zoning, although vascular “islands” are a prominent feature. Finally, fibrosis is not often a conspicuous feature, and may be entirely absent.

In contrast, the rheumatoid nodule, as seen in adults, is clearly arranged in three zones. There is an outer zone of fibrosis with considerable infiltration by lymphocytes, plasma cells, sometimes polymorphonuclears, and rarely eosinophils. The innermost zone comprises necrotic debris, sometimes containing fibrinoid material but more usually a grumous granular mass with fibrin, fibrinoid, and swollen collagen fibres mixed in it, sometimes containing nuclear debris, fat globules, and cholesterol clefts. Between the inner and outer zones lies a well-orientated layer of palisade cells, fibroblasts with large nuclei forming a compact border to the necrotic centre zone (Fig. 2, opposite). While there is some overlap in their individual features, a correct histological diagnosis can be made in nearly every case (Bennett and others, 1940, give a figure of 68 correct diagnoses in 69 patients with a firm diagnosis and one wrong diagnosis in a patient in whom the clinical diagnosis was somewhat doubtful). The exceptions show a mixed picture which gives the pathologist difficulty and leads him to issue an uncertain report. This usually corresponds to rather atypical features in the clinical presentation. It is uncommon for the pathologist who is familiar with this field to make a wrong diagnosis.

In juvenile rheumatoid arthritis, however, we have been surprised to find over the last 10 years that the nodule resembles closely that of rheumatic fever, and we have therefore surveyed all our nodule material and correlated the findings with clinical data. Apart from Findlay (1931), who illustrates a nodule from a probable case of Still’s disease resembling those of rheumatoid arthritis, we have found no reference to such a surprising finding in the extensive literature on rheumatic and rheumatoid nodules (reviewed up to 1938 by Keil (1938); and more recently by Horwitz (1949)).

Material and Methods

Material was available from the following sources:

1. Twelve cases of Still’s disease or juvenile rheumatoid arthritis with onset at or before the age of 16 years.
2. 57 cases of rheumatic fever (age range 3 to 49 years, including ten cases up to 10 years and ten cases aged 21 and over, all except twelve being below the age of 16).
3. 22 cases of adult rheumatoid arthritis (age range 20 to 73 years, all except one being aged 37 or over).

This material was reviewed against a general background of over seventy nodule examinations at the Postgraduate Medical School (unlisted and mostly from adult patients with rheumatoid arthritis or rheumatic fever).

After formol-saline fixation, routine paraffin sections (stained with haematoxylin and eosin, thionine, periodic acid Schiff, Gomori’s silver impregnation, Mallory’s phosphotungstic acid haematoxylin, and occasionally by Weigert’s elastin stain and Masson’s trichrome method) were surveyed, and the findings were tabulated in four grades (0-3), the patient’s name and clinical data being unknown. This grading was then correlated with the clinical diagnosis (based on detailed inpatient observation, serological studies, joint biopsies occasionally, and long-term follow-up), and with
SUBCUTANEOUS NODULES OF STILL'S DISEASE

Fig. 1.—Representative area of typical nodule from a typical case of rheumatic fever in a female aged 19. Haematoxylin and eosin ×163.

Fig. 2.—Representative area of typical nodule from a typical case of adult rheumatoid arthritis in a man aged 40. Haematoxylin and eosin ×160.
the age, sex, duration of disease, erythrocyte sedimentation rate, and Rose-Waaler differential titre (performed by Dr. Francis Scott using a slight modification of the original method: Scott, 1952).

Nine of the twelve cases of Still's disease showed gross multiple erosions at follow-up, and one of the remaining three showed a positive joint biopsy. All the last three showed repeatedly negative Rose tests and permanent residual deformities.

Results

The results are tabulated in two ways (Table 1):

(1) The percentage of patients showing each feature in each group.
(2) The mean grade for each feature in each group.

The only feature in the Still's disease group in which the findings resembled those in the adult rheumatoid arthritis group was fibrosis. Here, both the incidence and the mean amount of fibrosis was greater than in rheumatic fever, although not so great as in adult rheumatoid arthritis. Otherwise, the nodules of Still's disease resembled and in most instances were indistinguishable from those of rheumatic fever, showing absence of necrosis and palisading and the presence of oedema, well-marked vascular islands, and a fibrinoid lattice (Figs 3-6).

In only one instance was a diagnosis of rheumatoid arthritis made. This nodule came from the elbow of a boy aged 13 years whose rheumatoid arthritis had started at the age of 5 years. The disease was still active with an erythrocyte sedimentation rate of 71 mm./hr and a Rose-Waaler differential titre of 1:32. The nodule showed fibrosis (Grade 3), some necrosis (Grade 1), and a Grade 2 palisade (Fig. 7, overleaf).

Only one other boy (aged 14, onset of arthritis at age 7 years) showed palisading, but in this case the other features (Grade 3 fibrinoid lattice, etc.) were such as to suggest a diagnosis of rheumatic fever.

By contrast, in the adult rheumatoid arthritis group, twenty out of 22 were correctly diagnosed: the two exceptions being diagnosed as "rheumatic fever" and "query rheumatic fever" respectively. The first was a girl aged 20 (onset at age 19 years, erythrocyte sedimentation rate 34 mm./hr, Rose-Waaler titre 1:64), who 4 years later showed typical erosions and deformities, and the second was a man aged 53 with bronchiectasis and rheumatoid arthritis of 8 months' duration (erythrocyte sedimentation rate 90 mm./hr, differential agglutination titre 1:64), who later showed typical bony erosions and deformities. The nodules appeared between 2 and 12 weeks before biopsy (Fig. 8, overleaf). In neither of these cases was there necrosis, fibrosis, or palisading, although fibrinoid lattice was present.

In the larger group of rheumatic fever nodules, the only case incorrectly diagnosed as rheumatoid arthritis was a boy aged 8 with typical rheumatic fever and chorea for 2½ months (raised antistreptolysin-O titre, and an erythrocyte sedimentation rate which had fallen from 33 to 15 mm./hr), who was left at the time of biopsy with residual apical systolic and diastolic murmurs. This nodule showed some fibrosis, Grade 2 necrosis, and Grade 1 palisading, with no fibrinoid lattice (Fig. 9, overleaf).

### Table 1

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Cases</th>
<th>Features Examined</th>
<th>Fibrosis (Grades 0-3)</th>
<th>Palisade (Grades 0-3)</th>
<th>Necrosis (Grades 0-3)</th>
<th>Oedema (Grades 0-3)</th>
<th>Vascular Islands (Grades 0-1)</th>
<th>Fibrinoid Lattice (Grades 0-3)</th>
<th>Histological Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatic Fever</td>
<td>57</td>
<td>Percentage Present</td>
<td>33</td>
<td>19</td>
<td>10</td>
<td>74</td>
<td>89</td>
<td>91</td>
<td>Rheumatic Fever 56</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean Grade</td>
<td>0.4</td>
<td>0.3</td>
<td>0.1</td>
<td>1.2</td>
<td>—</td>
<td>2.3</td>
<td>Rheumatoid Arthritis 1</td>
</tr>
<tr>
<td>Age 16 or Under at Onset</td>
<td>12</td>
<td>Percentage Present</td>
<td>83</td>
<td>17</td>
<td>8</td>
<td>75</td>
<td>91</td>
<td>100</td>
<td>Rheumatic Fever 11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean Grade</td>
<td>1.3</td>
<td>0.4</td>
<td>0.1</td>
<td>1.0</td>
<td>—</td>
<td>2.2</td>
<td>Rheumatoid Arthritis 1</td>
</tr>
<tr>
<td>Age 17 or Over at Onset</td>
<td>22</td>
<td>Percentage Present</td>
<td>91</td>
<td>87</td>
<td>91</td>
<td>14</td>
<td>27</td>
<td>59</td>
<td>Rheumatic Fever 2 Rheumatoid Arthritis 20 (DAT + 20/21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean Grade</td>
<td>2.2</td>
<td>2.0</td>
<td>2.5</td>
<td>0.2</td>
<td>—</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>
**SUBCUTANEOUS NODULES OF STILL'S DISEASE**

Figs 3-6.—Representative areas of typical nodules from four typical cases of Still's disease, aged 8, 10, 15, and 16 years.

Haematoxylin and eosin.

---

**Fig. 3.**—Patient aged 8 years; D.A.T. 1:2. ×148.

**Fig. 4.**—Patient aged 16 years; D.A.T. 1:8. ×160.
Fig. 5.—Patient aged 15 years; D.A.T. 1 : 64. × 168.

Fig. 6.—Patient aged 10 years; D.A.T. 1 : 8. × 168.
I

SUBCUTANEOUS NODULES OF STILL’S DISEASE

Fig. 7.—Representative area from an atypical nodule of typical Still’s disease in a male aged 13 who had had rheumatoid arthritis for 8 years. Haematoxylin and eosin ×140.
(D.A.T. 1 : 32; Erosions + + .)

Fig. 8.—Representative area from an atypical nodule of typical adult rheumatoid arthritis in a male aged 53 who had suffered from rheumatoid arthritis for 8 months. Haematoxylin and eosin ×132.
(D.A.T. 1 : 64; Erosions + .)

Fig. 9.—Representative area from an atypical nodule of typical juvenile rheumatic fever in a male aged 8 who had suffered from rheumatic fever for 2½ months and was left with residual valvular lesions. Haematoxylin and eosin ×132.
Eight other patients showed Grade I palisading but this was associated with a bursal cavity in three and not associated with other features characteristic of rheumatoid arthritis. It should be noted that eleven of the 57 rheumatic fever nodules were biopsied at the stage of prenodular thickening (Bywaters and Horder, 1955), that is, before a definite nodule could be palpated; there were no gross histological differences between these and the fully-developed nodule except that fibrosis was absent in all but one and oedema usually present.

Correlation with Other Features.—Reliable data on the duration of the nodules were not available. Within the Still's disease group, there was no obvious correlation between the various histological features nor between any one such feature and clinical data such as age, duration of disease, erythrocyte sedimentation rate, or Rose-Waaler test. The only suggestive point was that two of the three cases of long duration (7 years and over) showed the only two examples of Grade 3 fibrosis. Similar analyses for the rheumatic fever and adult rheumatoid arthritis groups gave similar negative results. The Rose-Waaler test was positive in six of the twelve cases of Still's disease (a rather higher proportion than in our total cases of Still's disease), but showed no correlation with histology. In the adult rheumatoid arthritis group the test was positive in twenty, not done in one, and negative in one.

Discussion

The study confirms what others have noted, that it is usually easy to differentiate histologically between the nodule of adult rheumatoid arthritis and that of rheumatic fever. Nodules from cases with granuloma annulare (subcutaneous lesions) resemble fairly closely those of adult rheumatoid arthritis, as we have noted before (Bywaters, 1949). Nodules from four patients with acute lupus erythematosus and from one with an acute generalization of a disseminated discoid lupus erythematosus without rheumatoid arthritis, were variable in appearance, some resembling the lesions of rheumatoid arthritis and some those of rheumatic fever (unpublished observation); on the other hand, the nodules sometimes found in Schönlein-Henoch purpura resemble more closely those of rheumatic fever, as perhaps might be expected.

In Still's disease, however, arbitrarily separated from adult rheumatoid arthritis by an age at onset of 16 or under, the lesions closely resembled those of rheumatic fever in all but one of the twelve cases described here. If we accept the basic dictum of morbid anatomy that similar structural appearances mean similar pathological processes, these are grounds for considering the pathogenesis of rheumatoid arthritis once again (as was done by writers in the 1920s and 1930s) as similar to that of rheumatic fever. It is not merely a question of age, since adult rheumatic fever nodules resemble rheumatic fever in children, nor is it a question of duration of disease. An alternative hypothesis would be that Still's disease is a different entity from rheumatoid arthritis as seen classically in adults. Certainly it differs in many respects: in our series of over 200 cases of Still's disease seen here over the last 10 years, pyrexia is twice as frequent as in adults, rash is six times more frequent, and splenomegaly and pericarditis are twice as frequent. On the other hand, both nodules and the presence of a positive Rose-Waaler titre are only one-third as frequent as in the rather specialized group of adults with rheumatoid arthritis seen here. Table II contrasts the findings in a group of 197 cases of Still’s disease seen up to 1955 with those in a similar group of cases of adult rheumatoid arthritis seen here in the same period, but consisting of rather more unusual cases than are seen in a general hospital. However, the fact that all the manifestations of childhood disease, including that mentioned above and neck involvement, are seen from time to time in adults, and the fact that the Rose-Waaler test was positive in six out of twelve of these patients with nodules, renders it more likely that the disease is the same in both age groups and that the differing manifestations are due to the changes in “soil” with age.

<table>
<thead>
<tr>
<th>Percentage Cases with</th>
<th>Rheumatoid Arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age 16 or Under at Onset (197)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>62</td>
</tr>
<tr>
<td>Rash</td>
<td>31</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>26</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>8</td>
</tr>
<tr>
<td>Iritis</td>
<td>6</td>
</tr>
<tr>
<td>Nodules</td>
<td>9</td>
</tr>
<tr>
<td>Positive Rose-Waaler Test</td>
<td>13</td>
</tr>
<tr>
<td>Normal Erythrocyte Sedimentation Rate</td>
<td>15</td>
</tr>
</tbody>
</table>

As a corollary, it seems that the manifestations of rheumatoid arthritis are rather more dependent upon age change than those of rheumatic fever, although, of course, certain differences in the clinical manifestations of rheumatic fever in the young and in the old are well recognized. No differences could be seen in the patients with Still’s disease who had nodules between those with and those without...
SUBCUTANEOUS NODULES OF STILL'S DISEASE

a negative Rose-Waaler test. The course and outcome were variable in each of these sub-groups. However, the Rose-Waaler test was more preponderantly positive (as might be expected from analogy with the adult condition) in the group of twelve cases with nodules than in the remaining 200-odd patients with Still's disease without nodules.

Summary

Subcutaneous nodules from 91 patients, with rheumatic fever (57 cases), rheumatoid arthritis with onset at age 16 or under (12 cases), and rheumatoid arthritis with onset at age 17 or over (22 cases), were first reviewed without reference to clinical history or diagnosis and were then correlated with the clinical data.

The nodules from the younger group of patients with rheumatoid arthritis (Still's disease) closely resembled those from patients with rheumatic fever and, apart from a slightly greater frequency of fibrosis, did not resemble those from adults with rheumatoid arthritis except in one instance. The Rose-Waaler test was positive in six out of the twelve cases of Still's disease.

In the 22 cases of adult rheumatoid arthritis (where the Rose-Waaler test was positive in all but one), only two nodules showed a picture resembling rheumatic fever rather than rheumatoid arthritis.

The implications of these findings are discussed.

We are grateful to Dr. Francis Scott for the Rose-Waaler titrations and to Mr. P. J. Fiske for the microphotographs.

REFERENCES


Nodules souscutanés dans la maladie de Still

Résumé

On étudia les nodules souscutanés de 91 malades, atteints de rhumatisme articulaire aigu (57 cas), d'arthrite rhumatismale ayant débuté à l'âge de 16 ans ou en dessous (12 cas) et d'arthrite rhumatismale ayant débuté à l'âge de 17 ans ou plus (22 cas). Les résultats furent d'abord considérés en dehors des antécédents cliniques et diagnostiques et rapportés ensuite aux donnés cliniques.

Les nodules des malades jeunes atteints d'arthrite rhumatismale (maladie de Still) ressemblaient de près à ceux des malades atteints de rhumatisme articulaire aigu et, à l'exception de la fibrose un peu plus fréquente, ne ressemblaient pas à ceux des adultes atteints d'arthrite rhumatismale, sauf dans un cas. La réaction de Rose-Waaler était positive dans six sur douze cas de maladie de Still.

Dans 22 cas d'arthrite rhumatismale adulte (avec la réaction de Rose-Waaler positive dans tous les cas, sauf un), deux nodules seulement présentaient un tableau ressemblant celui rencontré dans le rhumatisme articulaire aigu, plutôt que dans l'arthrite rhumatismale.

On discute les implications de ces résultats.

Nódulos subcutáneos en la enfermedad de Still

Sumario

Se estudiaron los nódulos subcutáneos de 91 enfermos con reumatismo articular agudo (57 casos), artritis reumatoide empezada a la edad de 16 años o antes (12 casos) y artritis reumatoide empezada a la edad de 17 años o después (22 casos). Se consideraron los resultados primero fuera de los antecedentes clínicos y diagnósticos y luego en relación a los datos clínicos.

Los nódulos de los enfermos jóvenes con artritis reumatoide (enfermedad de Still) se parecieron mucho a los de los enfermos con reumatismo articular agudo pero, con excepción de fibrosis algo más frecuente, no se parecieron a los nódulos de los adultos con artritis reumatoide, salvo en un caso. La reacción de Rose-Waaler fue positiva en seis de los doce casos de enfermedad de Still.

En 22 casos de artritis reumatoide adulta (con la reacción de Rose-Waaler positiva en todos los casos, salvo uno) dos nódulos sólo presentaron un cuadro encontrado en el reumatismo articular agudo.

Se discuten las implicaciones de estos datos.