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ANTITUBERCULOUS TREATMENT OF ERYTHEMA INDURATUM BAZIN

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Abstract. The effect of antituberculous treatment in erythema induratum Bazin was studied in 72 patients. Fifty-two patients received INH alone and the remaining 20 were given streptomycin and/or PAS in addition. A control series of patients with EIB not treated with antituberculous drugs was not available. The nodules resolved within 12 months in all but four cases. Relapses were encountered in about one-third of the patients during a follow-up period of 8 months to 14 years (average 6.5 years). Resolution was more rapid and the rate of relapse somewhat lower after combined therapy than after monovalent treatment with INH. Moreover, the frequency of relapse decreased with increasing length of treatment. Similar results were obtained in patients with past or present tuberculosis and in those in whom no evidence of tuberculosis could be found. Active tuberculosis was diagnosed in 11 out of 72 patients. In addition, 25 patients had previously had tuberculosis. Thus a careful search for tuberculosis is indicated in every case of EIB. Combined antituberculous therapy for at least 12 months is suggested, irrespective of whether the examinations have revealed tuberculosis or not.

The term erythema induratum was introduced by Bazin (2) in 1861 and subsequently this condition has generally been connected with tuberculosis. Latterly, doubt has been cast (4, 7, 10, 14, 18, 22, 23, 24) on the role of tubercle bacillus in evoking erythema induratum Bazin (EIB), but the use of antituberculous drugs is still recommended (1, 3, 19, 21). However, reports dealing with the effect of this treatment are scanty and the number of patients concerned is small (6, 7, 9, 12, 13, 16, 20). The observation of lymphographic changes compatible with tuberculous lymphadenitis in the retroperitoneal space of several patients with EIB (11) as well as other recent findings (8, 9, 17) which support the assumption that, in some of the cases at least, EIB is a tuberculid, led us to undertake a more extensive study on the effect of antituberculous drugs on this condition.

MATERIAL AND METHODS

The series consisted of 72 patients with active EIB examined and treated at the Department of Dermatology, University Central Hospital, Helsinki, in 1955–1969. Nine of the patients were men and 63 women. At their first visit to the clinic, the mean age of the patients was 43 years (18–72 yrs) and the mean duration of their disease 2.9 years (1 mo. – 15 yrs). For details, see Table I.

The diagnosis was based on the clinical and histological findings and the result of the Mantoux test. In most cases the clinical picture of the nodules was typical of EIB with or without ulceration (Table II). The sharply defined, cold, subcutaneous nodules or infiltrations, bluish or brownish red in colour, and measuring 1 to 5 cm in diameter or even more, occurred predominantly on the calves, and, if multiple, were often in different stages of development. A biopsy from the lesions was obtained from every patient, and in 48 instances revealed all the histopathological features typical of EIB (tuberculoid infiltration, caseation necrosis and vascular changes). In 24 patients typical caseation necrosis was lacking, but tuberculoid infiltrates and vascular changes were present in every patient.

Before antituberculous treatment was instituted, the following additional examinations were performed: Physical examination, including palpation of peripheral lymph nodes, X-ray of the chest, routine blood and urine tests, and estimation of serum GOT and alkaline phosphatase. Sputum and urine were cultured for tubercle bacilli in 43 patients. Biopsies were taken from enlarged peripheral lymph nodes, and in 5 patients the histological picture indicated active tuberculosis. In 12 cases lymphography of the retroperitoneal lymph nodes was performed. All these examinations revealed active tuberculosis in a total of 11 cases. In addition, a history or signs of past infection were present in 25 patients (Table III). None of the patients had lupus vulgaris.

Antituberculous therapy consisting of isoniazid (INH) was given to all patients and 52 received this treatment alone. In addition to INH, 20 patients received para-aminosalicylate (PAS) and/or streptomycin (SM). The dosage of INH was 5 mg/kg body weight/day, while that of PAS corresponded to 12 g of free acid per day divided into three doses. SM was given intramuscularly, 1 g once a day for 2–5 months. Pyridoxine (vitamin B_6) was administered together with INH in some cases. The

Table I. *Duration of the disease and age of the patients on attending the clinic for the first time*

Age of patients	Duration of the disease (y.) <1	1–3	4–10	>10	Total
–25	4	2	3	—	9
26–35	10	2	3	—	15
36–45	7	3	5	1	16
46–55	10	2	2	3	17
56–65	5	2	5	—	12
66–	2	—	—	1	3
Total	38	11	18	5	72

intention was to extend the medication over a period of at least 10 months. However, in 23 patients the treatment was interrupted as unnecessary by the patient when the lesions had resolved, or was discontinued by the physician because of side effects, such as drug eruptions, nausea, vomiting or pathological liver function tests.

In most instances the ulcers were treated topically with oxytetracycline in ointment once a day.

In 62 patients a follow-up examination was performed 8 months to 14 years (mean 6.5 yrs) after the medication was discontinued. The remaining 10 patients are still under treatment. In connection with the post-treatment examination a new X-ray of the chest was taken and the Mantoux test and blood and urine tests were performed. Serum GOT and alkaline phosphatase levels were also determined.

RESULTS

The EIB lesions disappeared within 12 months of antituberculous treatment in 68 out of 72 patients (Table IV). The nodules resolved more quickly during combined treatment than during monovalent treatment with INH. The four patients whose lesions did not heal within one year had all received INH exclusively. Three patients with active tuberculosis had for some reason been treated with INH alone, whereas the remaining 8 patients with active tuberculosis received combined therapy. In spite of the active tuberculosis, the lesions healed within 12 months in all these patients.

During the follow-up period relapses occurred in 24 of the 62 patients. The rate of relapse was somewhat higher among those treated with INH alone than in those receiving combined therapy. In the INH group, 8 of the 10 patients treated for 6 months or less had a relapse, in six of them during the first two years after treatment. Those four patients in whom new nodules occurred in spite of 12 months of treatment are included in the group showing relapse within less than one year. Among the patients treated with INH for at least 10 months, relapses occurred less frequently, being seen in 11 out of 34 patients. The same trend was observed among those treated

Table III. *Frequency of tuberculosis, past or present, in 72 cases of active EIB*

Organ	No. of cases involved	Per cent
Lungs	30	42
Cervical lymph nodes	9	13
Retroperitoneal lymph nodes	3/12	25
Other organs	4	6

Table IV. *Response to antituberculous treatment*

Treatment	Time required for resolution of nodules (mo.) –3	4–6	7–9	10–12	No result	Total
Isoniazid alone	19	20	5	4	4	52
Combined therapy	14	5	—	1	—	20
Total	33	25	5	5	4	72

Table II. *Composition of the series*

Clinical picture	No. of patients	Males	Organ TB	TB in family	Histology Typical	Atypical
Calves						
Ulcerating	45	7	22	23	33	12
Non-ulcerating	15	2	8	5	8	7
Other sites on the legs						
Ulcerating	5	—	3	2	4	1
Non-ulcerating	7	—	3	3	3	4
Total	72	9	36	33	48	24

Table V. *Frequency of relapse correlated with type and duration of antituberculous treatment (ten patients still under treatment not included)*

Treatment	Relapse, years after treatment				Cured, follow-up period (y.)				Total
	<1	1–2	3–5	>5	<1	1–2	3–5	>5	
INH alone, months									
–3	2	1	—	—	—	—	1	—	4
4–6	2	1	—	2	—	—	—	1	6
7–9	—	—	—	—	—	—	—	2	2
10–12	2[a]	1	2[b]	1	1	6	3	5	21
13–	3	—	2	—	1	1	3	3	13
Total	9	3	4	3	2	7	7	11	46
Combined therapy, months									
–3	—	1[a]	—	—	—	—	2[a]	2	5
4–6	1	—	2	—	—	—	—	3	6
7–9	—	—	—	—	—	—	—	—	—
10–12	—	—	—	—	—	1[a]	—	1	2
13–	1[a]	—	—	—	—	1[a]	—	1	3
Total	2	1	2	—	—	2	2	7	16

[a] Active tuberculosis in one patient.
[b] Active tuberculosis in two patients.

with a combination of several antituberculous drugs: the nodules recurred in 4 of the 11 patients treated for 6 months or less but in only 1 of the 5 patients treated for at least 10 months. This exceptional patient will later be presented in detail.

Of the 11 patients with active tuberculosis, 3 are still under treatment. In 5 of the remaining 8 patients with active tuberculosis the lesions of EIB recurred (Table V). All three patients treated exclusively with INH belonged to the group showing recurrence of the lesions. The same applies to a patient treated with a combination of several antituberculous drugs but for less than three months. The fifth case was a woman of 37, in whom pulmonary tuberculosis had been diagnosed as long ago as 1948. She had been treated with INH, PAS and/or SM for two years before the first attack of EIB occurred in 1961. Simultaneously with the appearance of ulcerating nodules the pulmonary tuberculosis was found to be active. Therefore, combined therapy was again administered for two years. The lesions on her legs healed within one year, but two months after the treatment was discontinued new nodules appeared. Since then, antituberculous drugs have been given for short periods, but nodules still appear occasionally.

The results of the quantitative Mantoux test before and after treatment are given in Table VI. In 21 patients the sensitivity to tuberculin after treatment was at the same level as before treatment. In 9 patients it had increased and in 27 patients decreased.

DISCUSSION

During the last decade a tendency to challenge the tuberculous origin of erythema induratum Bazin has prevailed (4, 7, 10, 14, 18, 22, 23). Moreover, the correctness of classifying EIB as a condition separate from other types of nodular cutaneous vasculitis has been doubted (4, 10, 14, 18, 22). Pierini and his co-workers (18) even proposed the name "idiopathic lipogranulomatous hypodermitis" for Bazin's erythema induratum, Darier-Roussy's hypodermal sarcoid, nodular vasculitis, Weber-Christian's panniculitis and Makai's subcutaneous lipogranulomatosis, which they considered to be variants of one fundamental entity.

In our opinion the characteristic clinical picture of EIB distinguishes this condition from other forms of necrotizing cutaneous vasculitis and panniculitis, and we consider the unifying of these disorders a step backwards rather than forwards. Even the depressed or smooth peripherally pigmented scars seen in follow-up examinations of treated cases of EIB are highly characteristic. There are naturally "borderline" cases in which the clinical features alone cannot be considered diagnostic. In such cases the histology of the lesions and the result of the Mantoux test may provide valuable diagnostic supplements. However, the histological findings are highly dependent on the stage of the nodules and the site from which the biopsy is obtained, and therefore the

Table VI. *Tuberculin sensitivity in active and inactive stage of disease*

Mantoux test positive (T. U.) at follow-up examination	Mantoux test positive (T. U.) in active stage of disease					Total
	0.01	0.1	1	10	Not performed	
0.01	8	7	—	—	—	15
0.1	12	11	2	—	2	27
1	3	9	2	—	1	15
10	1	1	1	—	—	3
Not performed	2	6	4	—	—	12
Total	26	34	9	—	3	72

picture often varies in successive specimens taken from the same patient.

Evidence of past or present tuberculosis was found in half the patients of our series. The high frequency of active organ tuberculosis, 15%, can hardly be a coincidence, but, on the other hand, it does not prove that all cases of EIB are tuberculous in origin. Our recent finding of lymphographic changes compatible with tuberculosis of the retroperitoneal lymph nodes in four out of 16 cases (11) shows that a very thorough search for active tuberculosis is indicated in every case of EIB.

Original studies dealing with the effect of antituberculous treatment in EIB are scanty and the series are small. In preliminary reports dating from the first few years after the introduction of INH in 1952, the response to antituberculous treatment was ordinarily considered favourable (6, 13, 16, 20).

Feiwel & Munro (9) recently reported 12 cases of EIB. They found that the symptoms improved within 2 months and new lesions did not appear after 4 months of antituberculous treatment. Unfortunately, the follow-up period in their study was short, only 7 months to 2 years from the start of treatment, and therefore the final response to the therapy could not be assessed. Eberhartinger (7) reported 192 cases, 110 of which were treated with antituberculous drugs, but no exact data were given concerning the dosage of the drugs, duration of treatment, number of patients in the various therapy groups and results obtained. However, he stated that antituberculous drugs as well as tetracycline had a favourable influence on the lesions, although the frequency of relapses was not reduced. Krakauer (12) reported two cases treated with INH. In one of them the medication had to be interrupted after two months because of untoward effects, although the effect on the lesions was favourable. The other patient was resistant to treatment continued for 8.5 months.

In our series the nodules resolved in most cases within 6 months of antituberculous treatment. Resolution was more rapid in the group receiving combined treatment than in the group receiving INH alone. Relapses were encountered in about one-third of the patients during an average follow-up period of 6.5 years. The rate is markedly lower than that observed in series not treated with antituberculous drugs. Eberhartinger (7), for instance, reported that prior to treatment 85 out of 114 cases (75%) had had two or more episodes of EIB within a period of 6 years.

In our study relapses were encountered somewhat more often in patients treated exclusively with INH than in those treated simultaneously with other antituberculous drugs. Moreover, a correlation was observed between frequency of relapse and duration of treatment. The patient whose nodules relapsed in spite of more than 12 months of combined therapy had probably developed resistance to INH during previous treatment for pulmonary tuberculosis. Otherwise, no significant difference was observed as to the effect of treatment between cases with present or past tuberculosis and those in whom tuberculosis could not be detected.

We have no experience of the effect of corticoids with or without antituberculous treatment on the nodules of EIB. Some authors have reported their findings in a few patients (5, 7, 15). According to them, corticoids may accelerate resolution, but they do not decrease the rate of relapses.

It may be concluded that there is insufficient reason to discard the diagnosis of EIB. In this condition active tuberculosis is present so frequently that it can hardly be a question of coincidence. Although the present investigation does not show that EIB always is a tuberculid, the results justify a prospective study in patients in whom all examinations, lymphography included, have failed to disclose any evidence of tuberculosis; patients born on odd days of the month would receive combined antituberculous therapy and those born on even days (i.e. ca. 50% at random) no treatment. Until such a study has been made, we suggest combined antituberculous treatment of EIB for at least twelve months, irrespective of whether the examinations have revealed tuberculosis or not.

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