

## ERYTHEMA INDURATUM (BAZIN) TREATED WITH ISONIAZID

Sven la Cour Andersen

*From the Department of Dermatology, Finsen Institute, Copenhagen, Denmark*

**Abstract.** A series of 34 patients with erythema induratum (E.I.) (Bazin) were treated with isoniazid (INH). Most cases were treated with 100 mg 3 times daily to a total of 120 g. During a follow-up period averaging 4 years there have been no recurrences and no major side effects were observed during the treatment. The majority of the patients had a history of tuberculosis, histological evidence of E.I. and a high tuberculin sensitivity. Almost half the patients exhibited tuberculous changes. The author points out the importance of obtaining deep biopsies, doing Mantoux tests and chest radiography, taking a careful history and performing a meticulous clinical examination in order to confirm the diagnosis.

Erythema induratum (E.I.) was first described by Bazin in 1858 (1). It seems by now almost generally accepted that E.I. may be defined histologically as a vasculitis in the basal part of the cutis and subcutis. The histological appearances are characteristic, consisting of nodular infiltrations with caseous necrosis, abscess formation, epithelioid cells, giant cells and vascular occlusive changes (11). Most of these criteria must be fulfilled if the diagnoses are to be confirmed and clinically there must be a history of tuberculosis, a high tuberculin sensitivity and if possible, cultures of tubercle bacilli from the lesions.

## MATERIAL

The material comprises 34 patients, 32 females and 2 males. The average age was 46 years (14-75 years). Ten patients had a family history of tuberculosis, while 19 had a personal history of tuberculous disease, i.e. tuberculous cervical adenitis or pulmonary tuberculosis.

The signs of E.I. had been present before the patients presented themselves for 1-3 years in half the cases, with a maximum duration of 12 years. The distribution is given in Table I.

In 29 cases the infiltrations on the legs were ulcerated, occurring most often bilaterally and more often posteriorly than anteriorly.

## TREATMENT

All 34 patients were treated with isoniazid (INH). The dosage in 27 cases was 100 mg 3 times daily. Thirteen patients had more than one treatment series; a few had a dosage as low as 50 mg daily when the INH therapy was first introduced in 1952. Some relapsed, but healed again when the treatment was resumed using a higher dosage. All patients were treated during 1952-1968.

The total dosage of INH for each patient averaged 146.4 g, minimum 44.3 g and maximum 153 g in each treatment series. The treatment was continued for an average of 17 months (5-26 months). In addition to the INH, 28 patients were also treated initially with para-aminosalicylic acid (PAS), an average of 2191 g, distributed over about 48 days, while 6 patients received only INH. One patient had 12 g of streptomycin in addition to INH and PAS. No side effects occurred in 15 patients, while 19 had complaints in the form of mild depression, dizziness, headache, paraesthesiae or dyspepsia. Eighteen out of these 19 patients were also receiving PAS. In one case this medication had to be discontinued, but INH did not have to be withdrawn in any case.

The average follow-up period was 50 months after the discontinuation of treatment (2-148 months), and no relapses were observed.

The patients were treated mainly on an out-patient basis, the majority first by carbon arc or mercury light treatment prior to the antituberculous medication. Traditional dermatological treatment was also administered, supplemented in 6 cases by supportive bandage, but no patient received supplementary carbon arc or mercury light treatment during the medication.

## INVESTIGATIONS

Biopsy specimens were removed in 31 patients. In 12 of these cases the histological diagnoses was E.I., while the

Table I. Duration of symptoms and signs before examination of the patients

| Duration        | < 1 year | 1 year | 2-3 years | > 3 years |
|-----------------|----------|--------|-----------|-----------|
| No. of patients | 12       | 5      | 12        | 5         |

Table II. *Treatment, histological findings, history and tuberculin sensitivity*

| Patient no.                    | 1     | 2     | 3     | 4    | 5     | 6     | 7     | 8     | 9     | 10   | 11    | 12   | 13  | 14    | 15    | 16    |
|--------------------------------|-------|-------|-------|------|-------|-------|-------|-------|-------|------|-------|------|-----|-------|-------|-------|
| Treatment, total dose g INH    | 174.4 | 117.9 | 141.2 | 80.9 | 322.2 | 116.7 | 177.1 | 120.0 | 160.0 | 82.7 | 297.6 | 44.3 | 120 | 220.3 | 177.6 | 190.7 |
| Treatment series               | 2     | 1     | 1     | 1    | 3     | 1     | 2     | 1     | 2     | 3    | 3     | 1    | 1   | 2     | 3     | 2     |
| Histological evidence of E. I. | +     | +     |       |      | +     | +     | 0     |       |       |      | +     | 0    | +   | +     |       |       |
| History of tuberculosis        | +     | -     | +     | -    | +     | +     | -     | +     | +     | +    | +     | +    | -   | +     | -     | +     |
| Mantoux (ptb.)                 | 2-4   | 3-5   | 1-4   | 2-4  | 4-6   | 2     | 3-5   | 4-5   | 2-5   | 2-5  | 2-4   | 3-5  | 3-5 | 2-5   | 2-5   | 1-4   |

specimens in the others showed vascular changes without caseous necrosis, but otherwise the appearance was consistent with E.I.

Cultures from biopsies done in 26 cases (in Löwenstein medium) were negative for tubercle bacilli. Culture of gastric lavage, done in all cases, was positive in one. Culture of the urine was negative for tubercle bacilli in all 34 cases. Other laboratory studies showed increased sedimentation rate in 27 patients (13-101 mm), a negative Wassermann reaction in 28 patients tested, normal serum creatinine and/or serum urea in all cases. Incidentally, haematological and urinary studies were performed at 1 week, 2 and 3 weeks, and 3 months after the institution of treatment and regularly during the treatment without showing any other abnormalities.

All the patients had chest radiography which showed pulmonary calcifications or inveterate tuberculosis in 15 instances while 4 patients showed non-specific changes. Radiography of the urinary tract was normal in all cases except one which showed a renal calculus. In 2 cases fungi were investigated in scrapings from the lower leg, but with a negative result in both.

The tuberculin test (Mantoux) was performed as graduated intracutaneous injections (2) in which the tuberculin sensitivity is expressed as the threshold value for intracutaneous reaction (the minimum tuberculin dose giving specific reaction). The result is stated by means of the so-called tuberculin exponent ptb. (similar to pH), i.e. the logarithm with opposed sign of the threshold value in mg. In other words, "ptb. = 5" means specific reaction to dose  $10^{-5} = 1$  divided by 100,000 mg, etc. The tuberculin used was "old tuberculin" in phenol saline.

Table II gives the relationship between treatment, histology, tuberculin sensitivity and history.

### COMMENTS

In the course of time many therapeutic studies have been undertaken, using i.a. ascorbic acid, calciferol (14), tetracycline (7) and steroids (15)

but none with convincing effect. On the other hand, antituberculous drugs have been successfully used in tuberculous diseases of the skin, not only in tuberculosis verrucosa cutis and in lupus vulgaris (4, 16) but also in E.I. For instance, Pasiczny (12) in 1954, treated 10 patients with INH and streptomycin. Three relapsed during a 4-9 month's follow-up period. In 1965 Feiwel & Munro (6) treated 12 patients with INH, PAS and/or streptomycin. During a 7-month follow-up period they observed one relapse.

Several authors (3, 5) have reported side effects in the form of pellagra-like signs with cutaneous changes as well as neurological complaints. In the present material there were no significant side effects in spite of a maximum dose of 297.6 g INH and no prophylactic vitamin B supplement being given.

The differential diagnostic problems were mainly the distinction of E.I. from other forms of nodular vasculitis. The discussion relating to this differentiation was primarily due to doubt about the tuberculous etiology. Although this now seems to be almost accepted, some investigations still entertain this doubt because of the difficulties of culturing tubercle bacilli from the lesions (10). However, Ito (8), using fluorescence staining, found tubercle bacilli in 7 out of 18 patients with E.I.

The occlusive vascular changes in E.I. are similar to those in other forms of nodular vasculitis, but other tissue changes (11), the striking frequency of a tuberculous history, the chronic, recurrent course, the clinical picture with the tender, nodular, ulcerating infiltrations and the high

| 17    | 18    | 19    | 20    | 21    | 22    | 23    | 24    | 25    | 26    | 27  | 28    | 29   | 30  | 31   | 32   | 33  | 34    |
|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-----|-------|------|-----|------|------|-----|-------|
| 120.1 | 258.9 | 122.5 | 121.1 | 143.6 | 118.7 | 125.6 | 119.1 | 105.3 | 118.6 | 120 | 274.5 | 61.3 | 120 | 91.5 | 84.3 | 126 | 201.5 |
| 1     | 2     | 1     | 1     | 1     | 1     | 1     | 1     | 1     | 1     | 1   | 3     | 1    | 1   | 2    | 1    | 1   | 2     |
| -     |       |       | +     | +     |       | +     | +     | +     |       |     |       | +    |     |      |      |     |       |
|       | -     | -     |       |       | 0     |       |       |       | -     | -   | -     |      | -   | -    | -    | -   | -     |
| +     | -     | +     | -     | -     | +     | -     | -     | -     | +     | +   | -     | +    | -   | -    | +    | +   | -     |
| 5     | 2-3   | 4-5   | 4     | 2     | 2     | 5     | 5     | 5     | 2-5   | 3-4 | 2-5   | 1-4  | 4-5 | 5    | 1-2  | 2-5 | 1-4   |

sensitivity to tuberculin justify the differentiation of E.I. from other types of nodular vasculitis. It is of great importance in the histological diagnosis not only to take a large number of biopsies, but also to make the biopsies sufficiently deep in order to gain an impression of changes at the junction between the cutis and subcutis.

Patients with cutaneous tuberculosis and tuberculous lymphomas nearly always have a tuberculin sensitivity of ptb. = 3-5.

Data on the duration of the spontaneous healing tendency are sparse, but in a Norwegian report from 1943 (9) relapses occurred in 47.5% of patients who had received no antituberculous therapy (29 out of 61) and who had been followed for an average of 5 years.

The effect of antituberculous drugs depends not only upon the dosage and the duration of treatment, but also, as far as INH is concerned, upon whether or not the patient is a rapid inactivator (13), as this diminishes the therapeutic effect. This may have been a factor in some of the present cases, notably those treated with low dosages.

With regard to treatment, various drugs have been tried but none with satisfactory effect except the antituberculous agents. However, some of these agents have led to complications, not only emergence of drug resistance, but also side effects, e.g. hearing impairment following streptomycin and dyspepsia following PAS; the present study being reported to demonstrate the advantages of INH therapy.

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Sven la Cour Andersen, M.D.  
Department of Dermatology  
Finsen Institute  
Strandboulevarden 49  
Copenhagen Ø  
Denmark