Interstitial pneumonitis and pulmonary vasculitis in a patient taking an L-tryptophan preparation

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ABSTRACT: A case is presented of interstitial pneumonitis and pulmonary vasculitis ascribed to the ingestion of an L-tryptophan preparation. An unintended rechallenge supported the causal relationship. There was neither myalgia nor peripheral eosinophilia. Bronchoalveolar lavage fluid contained 12% eosinophils but few were present in the surgical lung biopsy specimen. Lung infiltrates receded after withdrawal of the drug and treatment with steroids. Dyspnoea and pulmonary hypertension persisted. Cyclophosphamide had no effect. Sclerodermiform skin lesions appeared as a late sequel. Chromatographic analysis of the L-tryptophan revealed no suspect impurities.

Preparations of L-tryptophan, an amino-acid which has enjoyed increasing popularity as an antide pressant and a hypnotic, have recently been held responsible for an epidemic of the eosinophilia-myalgia syndrome. This is defined as a peripheral eosinophilia of at least 1000x10^9/l incapacitating myalgia and the absence of other causes of eosinophilia [1]. However, this syndrome appears to be only part of a spectrum of side effects associated with the ingestion of this amino-acid.

Case report

A 65 yr old caucasian male was admitted to the Cardiology ward on 4 December, 1989, because of progressive dyspnoea on exercise and cough without phlegm since the end of August. He was subfebrile and cyanotic. Crackles were heard over both lungs. There were no skin lesions. The chest X-ray showed extensive perihilar alveolar infiltrates. A presumptive diagnosis of congestive heart failure was made, but diuretics and digoxin brought only modest improvement and echocardiography and MUGA-scan showed normal left ventricular function. The advice of the chest physician was sought.

History and clinical examination ten days after admission revealed no clues. The drug history was at that time considered non-suspicious: he had been taking zopiclone since 1988 and trazodone since August, 1989. L-tryptophan, 3 g daily, had been introduced as a hypnotic on 7 July, 1989. The dose had been doubled somewhere in November. It had been discontinued on admission. The patient had smoked about 75 g tobacco per week for over twenty years. He had been a salesman in a clothes shop and had no special hobbies. A chest X-ray taken in 1984 was normal.

Sedimentation rate was 23 mm·h⁻¹. The leukocyte count was 15.2x10^9·l⁻¹ with 5% eosinophils. Blood chemistry was unremarkable. Autoimmune tests, infectious serology and cultures were unrevealing. The chest X-ray had only moderately improved and arterial oxygen tension (Pao₂) had risen from 5.1 to 8.3 kPa. Vital capacity was 81% and transfer factor 31%. On 15 December the patient was discharged at his own insistence and resumed the use of L-tryptophan.

Transbronchial biopsy, performed on 28 December, showed nonspecific septal infiltration with some lymphocytes, plasma cells and neutrophils and one site of bronchiolitis obliterans. It was considered nondiagnostic. Bronchoalveolar lavage yielded 270 cells·mm⁻³; the differential cell count was 6% neutrophils, 12% eosinophils, 28% lymphocytes and 54% macrophages. Lymphocyte typing was not obtained. The patient at that time refused surgical lung biopsy.

Five weeks later dyspnoea had become incapacitating and right heart failure was present. Pao₂ was 5.6 kPa. The chest X-ray had changed little (fig. 1, left). The white blood cell count was 9.4x10^9·l⁻¹ with 6% eosinophils. Right heart catheterization gave a pulmonary wedge pressure of 5 mmHg and a pulmonary artery mean pressure of 29 mmHg.
Fig. 1. – (Left) The patient's chest X-ray at the time of surgical lung biopsy shows mainly alveolar infiltrates in the mid- and lower lung fields, and a small pleural effusion to the right. (Right) After five weeks of steroid treatment the parenchymal infiltrates have cleared. The lung biopsy stitches are visible on the right.

Fig. 2. – Pulmonary artery with segmental transmural inflammation, most pronounced in the intima with extension of the lymphocytic infiltrate into the surrounding alveolar walls (haematoxylin-eosin, x 40).

Surgical lung biopsy now revealed a diffuse interstitial pneumonitis and segmental panvasculitis consisting of transmural infiltration by lymphocytes and some neutrophils; eosinophils were scarce. Inflammation and oedema were most marked in the subendothelial space. There was loose fibrosis of the intima and some hyperplasia of the media; no fibrinoid changes were found (fig. 2).

Anti-neutrophil cytoplasmic antibodies and precipitins against common antigens were negative. A renal and mesenteric artery angiogram was normal.

All medication was withdrawn and methylprednisolone, 125 mg daily, was instituted. Dyspnoea improved only modestly and right heart failure persisted, requiring diuretics. The chest X-ray cleared (fig. 1, right) but transfer factor stagnated at 30% and Doppler echocardiography estimated pulmonary artery systolic pressure at 40 mmHg. Cyclophosphamide was added on 20 April, 1990, while corticosteroids were tapered off. His condition remained unchanged and all treatment was withdrawn by 15 June. On 17 July nifedipine, 10 mg t.i.d., was prescribed. On 11 September there were
no clinical nor echocardiographic changes but his most recent control on 8 January, 1991, suggested improvement with an estimated pulmonary artery systolic pressure of 30 mmHg.

In December, 1990, the patient reported the gradual development of asymptomatic skin lesions, the first beginnings of which he had suspected during summer. On the trunk and the proximal part of the extremities there were multiple hyperpigmented and slightly indurated plaques ranging from 5–8 cm in diameter. On the lower part of the legs the skin felt indurated and was covered by many small follicular papules. The skin of the face, fingers and hands was spared. Biopsy of abdominal skin showed fibrosis in the upper layer of the reticular dermis. These findings were consistent with scleroderma.

Product investigation

In November, 1990, we obtained the container from which the patient’s pharmacist had prepared the tryptophan capsules. It had remained virtually unused for several months after warnings to the medical profession had reduced sales to a trickle. The container had been bought from the Belgian wholesale distributor Ceria, who informed us that they acquired the bulk powder from the Japanese Showa Denko Company.

To investigate the presence of contaminants in the L-tryptophan powder we analysed its chemical amino-acid composition on an amino-acid analyser and by gas-liquid chromatography. In the first assay an LC 5001 Biotronik amino-acid analyser was employed, using a physiological programme. The tryptophan samples were prepared in the following manner: tryptophan powder (250 μmol·L⁻¹) was dissolved in 0.1 N HCl and after 45 min equilibration no insoluble material remained. 100 μl samples, filtered before analysis, were applied on the column and eluted with a physiological buffer programme over 145 min. After ninhydrin coloration at 120°C absorbances at 570 nm were monitored. Tryptophan was the major constituent (88%); ammonia (6%) and valine (1.2%) were minor components. There were no other peaks present.

To support our findings, identical samples were analysed by gas-liquid chromatography. Filtered samples were derivatized to N-heptafluorobutyryl-N-propylester, suitable for gas-liquid chromatography on a capillary OV-1 column and detection by TSD-detector. Similar results were obtained as with the first method.

A further comparison was made with a sample of a pro-analysis pure tryptophan powder from Sigma Chemical Company, St. Louis, USA, where we obtained identical patterns.

Regarding the chemical amino-acid composition of the patient’s tryptophan powder we conclude to the presence of tryptophan as the major component in the absence of other suspect contaminants from protein sources.

Discussion

Respiratory involvement is common in the eosinophilia-myalgia syndrome: cough or dyspnoea were reported in 64% of patients and pulmonary infiltrates in 16% [2]. Interstitial pneumonitis and vasculitis were documented in eight users of L-tryptophan preparations [3–5]. Findings in our patients were similar. The time course of the illness paralleled the use of the drug, which included an unintended rechallenge. Trazodone and zopiclone are not known to cause lung damage. Leukocytoclastic vasculitis secondary to trazodone had been reported but pulmonary involvement in this type of vasculitis is usually limited and shows a different histologic pattern [6]. Left heart failure was ruled out initially by noninvasive methods and by right heart catheterization immediately before surgical lung biopsy. Hence, it seems justified to attribute this disease to the L-tryptophan preparation. The late appearance of sclerodermatous skin lesions is consistent with this diagnosis [7].

The manifestations of L-tryptophan disease may be more protean than initially suspected. Dyspnoea and eosinophilia without myalgia were mentioned in early reports [2]. Of seven cases of severe pulmonary involvement, including the present, myalgia was absent at presentation in three [3, 4]. Only bronchoalveolar lavage evidenced eosinophilia in our case. Thus, even in the absence of myalgia or eosinophilia L-tryptophan should be considered in the differential diagnosis of diffuse lung disease.

The treatment of L-tryptophan disease is problematic. Even after withdrawal of the offending preparation, many patients remain severely disabled. Whereas steroids seem to have a beneficial effect on pulmonary symptoms, their efficacy is not constant [4]. In our patient, the interstitial pneumonitis, as judged by chest X-ray, receded under steroids but his exercise tolerance did not improve in proportion. We attributed this to residual pulmonary vascular disease and hypertension. In analogy with established practice for other forms of vasculitis, cyclophosphamide was tried, without benefit. Reporting treatment failures such as this may spare other patients inefficient and sometimes harmful therapeutic trials [8].

The time course of the pulmonary disease in our patient and certain features of the eosinophilia-myalgia syndrome are reminiscent of the toxic oil syndrome [9, 10]. Contaminants have therefore been sought as possible responsible agents in L-tryptophan preparations. Indeed, the eosinophilia-myalgia syndrome has been strongly linked to L-tryptophan from a single production source [11, 12] and Belongia’s group actually discovered an unexpected substance in nine of twelve retail lots used by affected persons, the Japanese Showa Denko Company being identified as the manufacturer [11]. Although the preparation used by our patient stemmed from the same source, no suspect substances were found to be present. Our analytical methods, though differing from Belongia’s, were of comparable sensitivity. However, disappearance of the contaminating
substance by spontaneous decay cannot be excluded, keeping in mind the long storage period before it was obtained and analysed [10].

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References