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PLEURO-PULMONARY ALLERGIC REACTION TO NITROFURANTOIN

By

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Nitrofurantoin (Furadantin) can create two kinds of side-effects: 1) toxic; 2) allergic.

Slight to moderate side-effects of both kinds are quite common; severe side-effects, however, are rare. The most serious toxic side-effect is polyneuropathy caused by a dose too large in relation to the patient's renal function. The most serious side-effect of the allergic type is a syndrome, unique for nitrofurantoin, whose main effects are symptoms in the lungs. So far about 30 cases with acute and 6 with chronic pulmonary reactions have been described (20, 15). However, further cases are known and it is not unlikely that this allergic reaction occurs more commonly than the above-mentioned numbers indicate.

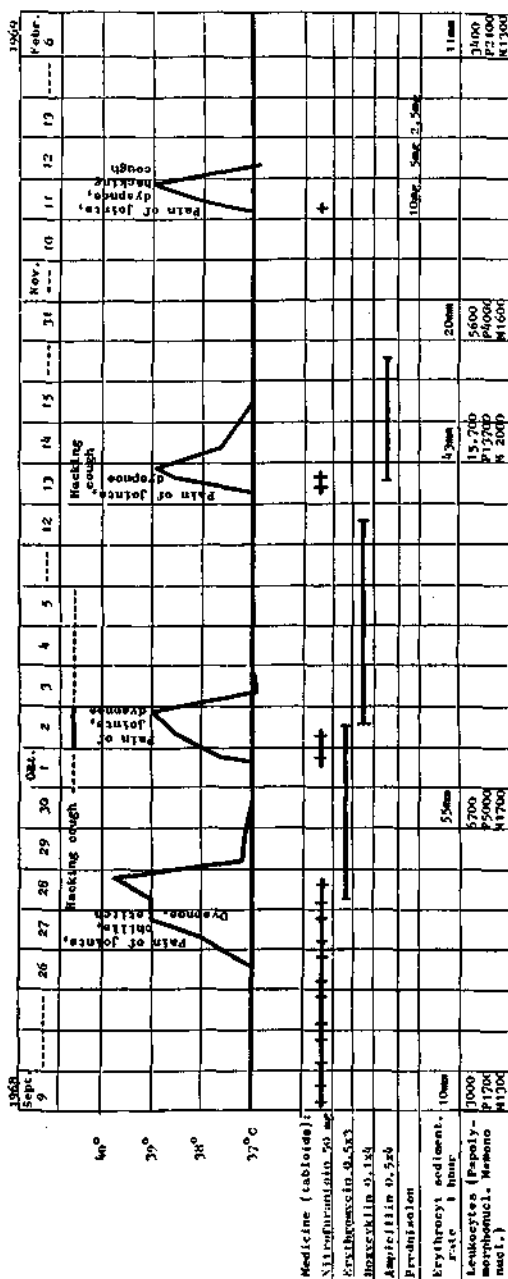
CASE REPORT

The case related here is a woman, aged 37, Para 3. Since the beginning of the 1950's she has been treated with sulfonamides on several occasions, for what was believed to be cystitis. Towards the end of her latest pregnancy in the spring of 1968 she suffered several attacks similar to those caused by renal calculi. Because of this, after delivery urography was carried out, and this showed irregular calyces and minor calcifications bilaterally, believed to be signs of earlier pyelonephritis. The patient had no fever, urine cultures gave negative results, erythrocyte sedimentation rate/1 hour was 10 mm and white blood corpuscles 3000/mm³ with 57 per cent polymorphonuclear cells. On September 9/68 long-term therapy with nitrofurantoin tablets in the relatively small dose of 50 mg $\times$ 2 was introduced as a safety measure. After 2 week's treatment the patient's temperature rose suddenly to 39.8° C, as can be seen from the diagram. At the same time she experienced general pain in her body which she localised in her joints, shivering chills, a stitch on deep breathing, manifest dyspnea and

a violent cough. In an upright position the cough became especially marked and occurred in prolonged attacks, during which cyanosis of the lips appeared. Crep- itant rales could be heard basally over both lungs. Blood pressure was normal and except for a tachycardia nothing remarkable was heard from the heart. Since pleuro-pneumonia was suspected, Erythromycin was introduced at the same time as nitrofurantoin was withdrawn. Surprisingly enough, the following morning the patient was almost without symptoms, except for some coughing. Lung X-rays showed that both costo-phrenic angles were shallow, and in the lateral position small amounts of free pleural fluid showed bilaterally. No path- ological changes could, however, be demonstrated in the parenchyma of the lungs. Erythrocyte sedimentation rate/1 hour was 55 mm, white blood cor- puscles 6700 with 64 per cent polymorphonuclear leucocytes. Nitrofurantoin was re-introduced on October 2nd. The next day the same symptom-picture with high temperature returned acutely. Nitrofurantoin treatment was suspended and she was given Doxycyklin. The following day the patient's condition had again improved dramatically. The same process, with similar results, was re- peated on October 13-14. Lung X-rays were now quite normal, erythrocyte sedimentation rate/1 hour was 43 mm, white blood corpuscles 15700 with 87 per cent polymorphonuclear cells (unfortunately, no differential calculation was made). At the end of October the white blood corpuscles presented a normal pic- ture and a sedimentation rate of 20 mm in 1 hour was noted. At that stage it was strongly suspected that nitrofurantoin was the cause of the pathological picture. To verify this a single 50 mg dose of nitrofurantoin was given on the morning of November 11th. 4 hours later the previous pathological picture returned, with high temperature, dyspnea and a dry cough. Prednisolone was administered, and the next day the patient was completely free of any complaint. Several months later erythrocyte sedimentation rate/1 hour was 11 mm and white blood corpuscles 3400.

DISCUSSION

This case correspond in almost every detail with the published ones with acute symptoms. The case first mentioned in the literature was reported by *Fisk* in 1957 (4). In addition to the symptoms mentioned, that patient had a moderate anaphyl- actic reaction with lowered blood pressure. A moderate de- crease in blood pressure has also been noted in some other patients (7, 13). In several of the reported cases there oc- curred copious frothy, white sputum, crepitating to harsh crackles over the lungs, especilly basally, where dull area by percussion and decreased breath sounds could be noted. On lung X-rays cloudy infiltrations appearing in patches were ob-



served, especially basally, often together with exudation in pleurae. Many symptoms thus indicate a acute noncardiac pulmonary edema (4, 5, 10, 11, 16). In only a few cases were signs of asthma observed (14, 19), viz. in patients with anamnesis of bronchial asthma. A strong feeling of illness, feebleness, pain in the chest and tachycardia also often enter into the pathological picture. In some patients there appeared at the same time pruritus, urticaria and exanthem (4, 7). In every case there existed leucocytosis, uppermost $25.000/\text{mm}^3$, with high neutrophilia, uppermost 95 per cent, and often more or less pronounced eosinophilia. In several cases, however, eosinophilia was lacking (4, 10, 11, 17, 18). Erythrocyte sedimentation rate/1 hour is usually normal, but in the case here clearly increased. Electrocardiograms and other heart examinations showed no remarkable findings except for tachycardia. In one case a scintigram was made, which showed greatly reduced radioactivity over the lungs while the attack was in progress, indicating a process in the pulmonary vessels (12). No fatal cases have so far been reported.

Differential diagnosis in several cases, especially among older patients, has been cardiac pulmonary edema and these patients were admitted to hospital as emergencies with this preliminary diagnosis. Other diagnoses which have been considered are pneumonia, pleuritis, tracheo-bronchitis, pulmonary embolism and Löffler's eosinophilia. The latter, however, is characterised by less pronounced symptoms.

As *Nicklaus & Snyder* (11) and others (5, 12) point out, there are several factors which indicate that the symptoms are caused by a acute noncardiac pulmonary edema, and that this can be explained by an allergic reaction in the walls of the fine pulmonary vessels. This allergic reaction (on provocation with a single dose of nitrofurantoin, for example) is briefly characterised as follows:

1. Acute symptoms with fever, chills, dyspnea, coughing and occasionally obvious symptoms of pulmonary edema.
2. A latency period of about 4 hours.

3. Rapid disappearance of symptoms about 6-24 hours after with-drawal of the preparation.
4. Pronounced neutrophilia, often combined with eosinophilia.
5. Shock organ most probably the walls of the fine pulmonary vessels.

Even if direct proof is missing, this type of allergic reaction corresponds most closely with Arthus's reaction, that is Type III reaction according to Gell & Coombs' classification. As an example in man, farmer's lung (extrinsic allergic alveolitis) can be mentioned which is considered to be caused by such a type of allergic reaction (21, 22). There are undeniably several symptoms common to both farmer's lung and the pulmonary reaction to nitrofurantoin. In the cases of Arthus's reaction (21, 22), precipitating complexes of antigens, antibodies and complement are formed. The activated complement acts leucotatically: granulocytes accumulate which phagocytose the complexes in the vessel walls. Tissuedamaging substances, such as proteolytic enzymes and histamine, are thereby released from the granulocytes. This results in edemas and on occasion even in diapedesis of red blood corpuscles and tissue necroses. The released histamine can cause an increased number of eosinophils, which are thought to inactivate histamine.

This theory can explain the symptom picture of the pulmonary reaction caused by nitrofurantoin, but why the reaction takes place principally in the vessel walls of the *lungs*, cannot be satisfactory explained. The great number of capillaries in the lungs may however play an important role (20, 21).

Rosenow et al. (15) have recently reported on 5 cases with slowly increasing dyspnea, usually without fever reaction, 6 months to 6 years after the introduction of daily nitrofurantoin treatment. Lung X-rays showed diffuse basal infiltrations, but no pleura exudation. Pulmonary function tests showed signs of restrictive ventilation reduction and reduced diffusion capacity. After nitrofurantoin was withdrawn and replaced by

treatment with steroids, there was an improvement in every case but one. Pulmonary biopsy showed chronic interstitial pneumonitis and fibrosis. The level of lactic dehydrogenase enzyme (LDH) was elevated in the three patients tested, indicating an active interstitial pulmonary disease with cell necroses. When the patients improved these values became normal.

David et al. (2) have described a similar case, viz. a seven-year-old child with chronic pulmonary symptoms of one years duration who had taken nitrofurantoin for three years before the reaction developed.

This type of more chronic pulmonary symptom during treatment with nitrofurantoin undeniably corresponds to the chronic form of farmer's lung.

Nicklaus et al. (11) noted increase in serum LDH even in a patient in the active stage of acute nitrofurantoin pulmonary reaction.

The elevated LDH-level in these patients confirms the hypothesis of an allergic reaction of the Arthus type, which, as have been mentioned, can result in tissue necroses.

SUMMARY

A case of allergic reaction to nitrofurantoin is described, characterised by acute development of fever, dyspnea, severe coughing, pleura exudations, leucocytosis and increased erythrocyte sedimentation rate. The diagnosis was established after the patient on 4 occasions after renewed treatment had developed the same symptoms, which rapidly disappeared on withdrawal of the preparation. There are about 30 similar cases with acute and 6 with chronic pulmonary reaction, previously described. A theory is put forward that this allergic syndrome unique for nitrofurantoin is caused by the Arthus reaction (Type III reaction according to Gell & Coomb's classification).

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