Superinfection with Mycobacterium tuberculosis in a patient with pulmonary alveolar proteinosis

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ABSTRACT

We present the case of a patient who was twice hospitalised in the National Institute of Pneumology „Marius Nasta”. At his first hospitalisation, the patient was diagnosed with alveolar proteinosis – treated in the classical method, i.e. with a bilateral pulmonary lavage; there was a significant improvement in the clinical condition, radiologically and paraclinically (arterial blood gas – ABG). 5 months after leaving the hospital, he came back with a noisy, dragging symptomatology and with the opacification of the left pulmonary field, the necessity of a new pulmonary lavage coming out. As a result of the investigations, an infectious disease – lung tuberculosis – was diagnosed; an extremely rare association in patients with proteinosis, with noncompromised immunologic status.

Although we established an antituberculous treatment, the general condition did not improve, confirming the existence of a Mycobacterium tuberculosis specimen, resistant to two antiTB drugs, even from the initiation. The evolution proved to be favourable at the introduction of an individualized schema of treatment.

It is a rare association of diseases, tuberculosis being in this case a nosocomial infection with a bacillus initially resistant to antiTB drugs.

The alveolar proteinosis is a rare pulmonary disease (1-2 cases/ 1 million persons), in most cases (> 90%) idiopathic, characterized by the accumulation in the alveolus of an amorphous material, granulated, PAS+ (seric proteins and phospholipid-lecithin, plus the proteins A and B which arises from surfactant). The interstice remains in general unaffected. The etiology is unknown, but 3 forms were described: the achieved one (idiopathic, autoimmune), the secondary one (of some malignant hematological diseases, exposure to noxious and infections) and the congenital one, all of them having basically the macrophage deficit, a GM-CSF deficit or the...

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SUPERINFECTION WITH MYCOBACTERIUM TUBERCULOSIS IN A PATIENT WITH PULMONARY ALVEOLAR PROTEINOSIS

The presence of antibodies against GM-CSF (granulocyte-macrophage colony-stimulating factor) is common. The beginning is pernicious, with dry cough (productive to smokers), physical asthenia, progressive dyspnea to effort, unsteady fever; many of the patients might be asymptomatic.

Paraclinically, the characteristic is the rising of LDH level; functionally: a restrictive ventilation dysfunction with decrease of the gas transfer through the alveolocapilar membrane and the ABG frequently indicating a moderate hypoxemia; on the chest radiography it can be observed nodular opacities with a "butterfly" disposition, with a localization mainly basal and on the tomodensitometry it could often be seen an image as a "frosted glass". A doubtless diagnosis is given by the visualization of PAS+ material from the bronchioloalveolar lavage obtained by bronchoscopy. The only known efficient treatment for the disease is the pulmonary lavage, successively on both lungs, performed under general anesthesia on an intubation probe with double lumen using 10-20 lt. of physiologic serum. Antibiotic treatment is administered prophylactically (for preventing an superinfection); on the congenital form a pulmonary transplant could be useful. Oxigenotherapy is inefficient. (1-6, 8-12)

CASE REPORT

We present the case of a 53 years old patient (man), a heavy smoker (52 PA), with professional exposure to wood powder. An insidious beginning of the simptomatology since about one year: progressive dyspnea to effort, initially a dry cough, afterwards with a mucous expectoration. Objectively, the patient was cyanotic when he was hospitalised; pulmonary he presented: basal bilateral dullness and crepitants at this level. Paraclinically: high hemoglobin (due to hypoxemia); 18,56 g/dl, with hematocrit 54,31% VSH of 23/63 mm/h/2h, suggesting an active inflammatory process. The ABG shows a severe hypoxemia with normocapnia (pH=7,42, PaO₂=32,6 mmHg and PaCO₂=46 mmHg).

Imagistically, on the standard chest radiography (Image 1) in the posteroanterior incidence it was noticed an unhomogeneous opacity, with indefinite outlines, of an alveolar type, situated in the medium and inferior fields. A computed tomography shows (Image 2) a diffuse bilateral interstitial infiltration (with large areas of diffuse interstitial infiltration, with a "frosted glass" aspect, and with perilobular, subpleural, peribronchovascular localization, with images of bronchial trajectories with aeric contents, visible in all the pulmonary segments) raising the suspicion of alveolar proteinosis.

A bronchoscopy was performed and it was undiagnostic, but the bronchoalveolar lavage (performed on the right superior lobar territory, the medium lobar and the right inferior lobar territory) emphasized numerous PAS+ corpuscles (Image 3).

The treatment for the alveolar proteinosis was a classic one: left pulmonary lavage (with 15 lt. physiologic serum), then the right one after 3 weeks (16 lt. physiologic serum), to which antibiotic with large spectrum was associated.
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The patient left the hospital with mild hypoxemia but with the value of the oxigen in the arterial blood superior to the one when he was hospitalised (pH = 7.41, PAO₂ = 56.8 mmHg and PACO₂ = 27.8 mmHg).

5 months after leaving the hospital, he came back with a rise of fever (38-38,5°C), purulent cough with mucopurulent expectoration, unselective inappetence, without ponderal decrease, a simptomatology progressively occured during 3 weeks, for which he received ambulatory treatment with cephalosporins of the II generation, but with no improvement. Objectively, the patient was feverish (38,9°C), pulmonary with crepitant rattles and a dullness on the left base. The chest radiography described an unhomogeneous opacity of the alveolar type which seized the inferior and superior field of the left lung (Image 4).

Paraclinically, the tests of the inflammation were higher (Fibrinogen 723 mg/dl, PCR 279,6 mg/dl) and at the ABG the value of the oxigen in the arterial blood was higher compared to the one at the moment of the previous hospitalisation (PaO₂ – 63.3 mmHg, PaCO₂ – 22.9 mmHg, pH – 7.43). Resuming the investigation, functionally it was ascertained a moderate restrictive ventilatory disfunction with a decrease of the vital capacity with 39% (at his first hospitalisation the patient could not be investigated functionally because of the severe hypoxemia) and bronchoscopically: – at the bronchioloalveolar lavage, PAS+ corpuscles have been no longer found, but the microscopic examination for BK from the bronchic aspiration, in concordance with the examination of the sputum, was intensively positive. Because at his first hospitalisation the patient proceeded from a sanatorium for tuberculosis, an treatment for tuberculosis, regimen II was initiated, resumed with 5 drugs: isoniazid (INH), rifampin, pyrazinamide (PZA), ethambutol, streptomycin – daily.

The patient continued to be feverish under the treatment, with an insignificant improvement of the cough and expectoration and at the control (made 2 months after the initiation of the treatment) the BK microscopic examination remained positive. The short series of drug sensitivity test (performed from the initial culture) showed resistance to INH and sensitivity to PAS (paramino-salycilic acid), which led to the modification of the therapeutic schema – individualized regimen (with rifampin, PZA, ethambutol, streptomycin, prothionamide, cycloserine, ciprofloxacin) and to the necessity of performing a drug sensitivity test on long series. This last one indicated a new resistance to streptomycin, leading to its removal from the treatment. With the new therapeutic regimen the evolution was favourable, with the disappearance of the fever, the evident improvement of the cough and expectoration and after 5 months of individualised treatment, along with the improvement of the radiological image (Image 5).
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DISCUSSIONS

The association between alveolar proteinosis and tuberculosis is extremely rare; up to now, only 4 cases have been published: two of them as superinfection of the proteinosis in the adult patients with acquired immune deficiency syndrome (7), one case in a HIV positive infected child (13) and one with the association proteinosis and diabetes mellitus (8). The fact that at his first hospitalisation he proceeded from a sanatorium (a hospitalisation of 8 weeks), where are treated mostly patients with tuberculosis, raised the suspicion that the infection occurred in this way. A fact upheld also by the long duration of the hospitalisation. Likewise, the hypothesis that the tuberculosis should have a primary resistance to antiTB drugs (infection with BK resistant to INH and streptomycin) is very plausible.

According to the National Tuberculosis Control Program (published by the Romanian Ministry of Health), the patients with pulmonary tuberculosis, at their first treatment, should receive the treatment of regimen I (isoniazid, rifampin, pyrazinamide, ethambutol on a daily administration in the first 2 months, then 3 days out of 7 in the next 4 months) (14).

We prefered the administration of the resumed regime II, which is usually administered to the patients who already had needed antiTB drugs treatment (isoniazid, rifampicin, pyrazinamide, ethambutol, streptomycin), daily for two months, followed by a month administration of the same schema – from which streptomycin was eliminated – and an administration of 5 months, 3 days out of 7 of isoniazide, rifampicin and etambutol, starting precisely from the premise that the patient could have been exposed to tuberculosis bacillus – some of them with various spectrum of resistance.

Testing the antibiotic resistance in patients at their first treatment is performed on short series (starting from the premise that the highest probability is that the infection has been produced with a bacillus with total sensitivity). This regards testing the spectrum of sensitivity to INH and rifampin (first- line agents, which have the highest risk of becoming ineffective due to BK resistance, the replacement in the schema being needed with other 2 new drugs) and PAS (which together with the catalase and nitratreductase test) differentiates Mycobacterium tuberculosis (M. Tuberculosis) from Mycobacterium bovis and atypic mycobacterium.

The susceptibility to PAS, concerning our patient, indicates the fact that there is an infection with Mycobacterium tuberculosis (Mycobacterium bovis and atypic Mycobacterium having a natural resistance to PAS). Tracing out the resistance to one of the drugs tested on the short antibiotic test leads mandatory to the proceeding of the antibiotic test on long series, estimating that it may simultaneously exist more than one resistance to antiTB drugs (fact confirmed in the case of our patient). In the case of patients with a resistance to first-line drugs, this one is replaced by other two from the second-line agents – with a prolongation of the treatment from 6 to 9 months. When it appears that there are two or more resistances, the treatment schema should be an individualised one, which would include minimum 3, preferably 5 drugs, to which the sensitivity is preserved for a duration of 2 years. (14) Strictly concerning the case of our patient, knowing initially only the sensitivity spectrum from the antibiotic test on short series and presuming the coexistence of other resistances, we prefered to introduce from the begining 3 new antiTB drugs (prothionanamid, cycloserine, ciprofloxacin); this is mandatory in order to avoid inducing new resistances during our treatment by replacing one antiTB drug with another (as determined by the antibiotic test on short series); this fact proved to be correct as the antibiotic sensitivity on long series (which is performed each time when is found out the resistance to the one on short series) did confirm also the resistance to streptomycin, the patient remaining in the therapeutic schema with 6 antiTB drugs after the elimination of streptomycin – enough to offer the chance of recovery.

The patient’s simptomatology at his second hospitalisation, respectively the 38° C fever, could be put so much on the account of the tuberculosis. At his first hospitalisation the patient had been unfeverish, in spite of the big quantity of PAS+ liquid from the alveolus, on both lungs. At the administration of antiTB drugs treatment regime II, it persisted, decreasing only after the individualised schema. This fact makes the fever be interpreted with the most probability as being the privilege of the polychemo-resistant tuberculosis.

Romania is a country with a raised incidence of pulmonary tuberculosis – 110 cases (100.000
inhabitants). So, our patient’s tuberculosis could have been a “community acquired” infection. The fact that our patient needed a long length hospitalisation in a hospital where most of the patients were receiving the tuberculosis treatment, the etiology of the disease should be found in the hospital medium – all the more so as we are dealing with a bacillus with resistance. These data make us also believe that the patient presented a pulmonary tuberculosis with initial resistance to isoniazid and streptomycin. The prognosis in this case is a good one – on short term, the patient receiving a treatment with enough drugs to which he presents sensitivity, so that, after 2 years of treatment we expect a recovery (fact sustained by the improvement of the radiological image at the 5 months control) (image 5); on a long term, however, the prognosis is uncertain (on the base that there is a deficit of a local defence, even if the patient is in a good immunologic status).

CONCLUSION

1. In this case report the Mycobacterium tuberculosis infection was superimposed on a rare pulmonary disease, alveolar proteinosis, which acted a predisposing factor.
2. The Mycobacterium tuberculosis infection was, with a very high probability, a nosocomial one. Even if in the pneumology departments we try to segregate the patients with tuberculosis from the others, sometimes this cannot be possible in all cases. More, our patient was incorrectly diagnosed initially with tuberculosis, so he came in contact in the specialised department, with those patients.
3. Mycobacterium infection, resistant to two drugs (INH and streptomycin), is related also to the failure of initial diagnosis, the patient coming in contact with the other chimioresistent drug patients.
4. Even if the radiologic examination and the istoric of professional exposure were concordant with a diagnosis of diffuse interstitial pneumopathy (e.g. allergic alveolitis), the positive diagnosis was rapidly established by bronchoscopy and bronchoalveolar lavage.

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