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Inadequate access to diagnostic resources: a case of unrecognised hypersensitivity pneumonitis

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Key words
Hypersensitivity pneumonitis; biological risk; air-conditioning

Parole chiave
Polmonite da ipersensibilità; rischio biologico; aria condizionata

Summary
Objective: *Hypersensitivity pneumonitis (HP) often goes unrecognized because of its relatively low incidence in the general population and it is frequently misdiagnosed as a respiratory infection or idiopathic interstitial lung disease.* **Methods:** *Through the analysis of a paradigmatic case of hypersensitivity pneumonitis, in which only symptomatic diagnosis and treatment were proposed, we argue that limiting the clinical process to generic diagnosis, without detection of the etiologic agent, makes it impossible to avoid exposure, hinders compensation and severely worsens the evolution of the disease.* **Results:** *In 1981, a previously healthy, 28-year-old female clerk developed respiratory symptoms. She was diagnosed as suffering from extrinsic bronchial asthma and was treated with steroids and broncho-dilators. Neither immunologic tests nor any environmental pathogen research were proposed until 2008, when precipitins analysis showed positivity to Thermoactynomyces vulgaris, which had presumably contaminated the centralized air-conditioning system.* **Conclusions:** *The diagnosis of HP is unlikely to be missed if, in all clinical settings, occupational or environmental causes are routinely considered in the differential diagnosis of any patient with a respiratory problem. This approach could provide a better clinical management of the disease and more effective programmes of primary prevention. Implicit rationing of healthcare resources by limiting diagnostic tests that are not readily accessible reduces patient autonomy and the benefits of medical care.*

Riassunto
«Accesso inadeguato alle risorse diagnostiche: un caso di polmonite da ipersensibilità non riconosciuta». **Obiettivo:** *La polmonite da ipersensibilità (HP) spesso sfugge alla diagnosi a causa della sua incidenza relativamente bassa nella popolazione generale ed è spesso confusa con infezioni respiratorie o malattie interstiziali idiopatiche del polmone.* **Metodo:** *Tramite l'analisi di un caso paradigmatico di HP, nel quale è stato effettuato solo il trattamento sintomatico, giungiamo alla considerazione che limitare il processo diagnostico alla diagnosi generica, senza identificare l'agente eziologico, rende impossibile evitare l'esposizione, impedisce l'indennizzo del lavoratore e peggiora*

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sensibilmente l'evoluzione della malattia. **Risultati:** *Nel 1981, una impiegata ventottenne precedentemente in buona salute sviluppa una sintomatologia respiratoria che viene interpretata come asma bronchiale estrinseco e trattata con corticosteroidi e broncodilatatori. Nessun test immunologico né alcuna indagine ambientale viene eseguita fino al 2008, quando la ricerca delle precipitine risulta positiva per Thermoactynomyces vulgaris, che aveva probabilmente contaminato l'impianto centralizzato di aria condizionata.* **Conclusioni:** *La diagnosi di HP non può sfuggire se nella diagnosi differenziale dei pazienti con problemi respiratori si tiene conto di tutte le possibili cause professionali e ambientali. Questo approccio fornisce un migliore trattamento clinico della condizione morbosa e consente di mettere in atto la prevenzione primaria. Evitare di prescrivere i test diagnostici meno comuni e non facilmente accessibili costituisce un razionamento implicito delle risorse sanitarie, che riduce l'autonomia del paziente e il beneficio delle cure.*

Introduction

Hypersensitivity pneumonitis (HP) often goes unrecognized because of its relatively low incidence in the general population. It is frequently misdiagnosed as a respiratory infection or idiopathic interstitial lung disease, depending on its clinical presentation (23). This variability in the clinical presentation pattern of HP is likely to lead to underdiagnosis, unless HP is considered as a diagnostic possibility in a number of different clinical settings (16).

Here we discuss a case of a 27 years overdue diagnosis of HP, in order to analyze the coherency of the diagnostic process and its consequences. The hypothesis is that the delay was due to two factors: 1) the lack of expertise in occupational medicine, and 2) the limited availability of diagnostic resources.

Case report

In 1981 a previously healthy 28-year-old female white-collar worker, a non-smoker, with no family or personal history of respiratory or allergic disorders, started to complain of episodes of fever with dry cough, dyspnoea, stuffy nose, dry throat, smarting eyes, conjunctival irritation, pulsing headache, and tachycardia. Chest X-rays taken in the initial phase of investigation, showed diffuse thickening of the broncho-alveolar design. Pulmonary function tests (PFTs) showed slight bronchial obstruction with reduction of the forced vital capacity (FVC) at middle and high expiratory volumes.

After undergoing several allergological tests, that proved negative, a prick test showed low-level positivity (+) for Dermatophagoides pter. and house dust, so the patient was diagnosed as suffering from extrinsic bronchial asthma. She was treated with oral and topical corticosteroids that resulted in a temporary, moderately positive response but failed to achieve complete recovery; in fact symptoms inevitably recurred more severe than before. The worker showed recurrent episodes of pyrexia (40°C) accompanied by shortness of breath, chest tightness, chills, and general malaise on the first day back to work after a break, generally in the afternoon. These symptoms were present for a few hours and dyspnoea was the only symptom that persisted in the following days. The febrile episodes were diagnosed as "bronchitis" or "pneumonia". Recurrent bouts led to hospital admissions and further medical examinations. High Resolution Computed Tomographies (HRCTs) performed during such episodes showed scattered areas of prominent interlobular thickened septa with a migrant pattern of bilateral patchy alveolar densities and interstitial infiltrates, for the most part in the lower lobes. Spirometry showed a restrictive pattern (decreased total lung capacity and vital capacity) with a slightly increased residual volume.

The acute symptoms, which were typically characterized by periods of remission and flare-up, oc-

curred in the workplace shortly after entering the office building but receded during weekends and long periods away from the workplace. The clinical pattern worsened until 2002, the year when the centralized air-conditioning system was dismantled and substituted by local air-conditioning devices.

Between 2002 and 2008 the subject manifested low-grade progressive dyspnoea and cough, malaise, anorexia and weight loss, with no systemic reactions and no obvious oscillation of the symptoms.

The patient was examined at our outpatients centre in February 2008, when she was 55 years old. She appeared in mild respiratory distress and reported excessive fatigue: body mass index was low (17.8), thus indicating underweight. Examination showed widespread coarse inspiratory crackles and expiratory wheezing. The clinical history clearly described the symptoms, their timing, and included a thorough investigation on the patient's environment that did not reveal any potential offending contact other than the occupational one.

From an accurate occupational and environmental anamnesis it emerged that she had worked, since 1978, as a judiciary registrar in Southern Italy, in offices with a poorly-maintained centralized air-conditioning system. The poor condition of the air conditioning system was demonstrated by the repeated complaints by the employees, of sufficient magnitude to elicit a union protest action. The employer did in fact carry out environmental investigations, of which unfortunately there is no documentation, and decided to change the system in 2002.

Chest X-ray showed a combination of lung fibrosis and emphysema. Lung diffusion capacity was decreased (DLCO=58%). Blood analysis showed hypoxemia with a normal PCO_2. The methacoline test was negative.

The details described supported a strong suspicion that a possible workplace contamination could have played a central role in the etiology of the disease, so we prescribed serum precipitating antibodies testing.

The patient's serum was tested by the double gel diffusion test in two dimensions (Ouchterlony technique) against: Penicillium species, Aspergillus species, *Thermoactinomyces vulgaris*, *Micropolyspora faeni* and Pigeon Serum with evidence of positive precipitin reaction against *Thermoactinomyces vulgaris*; specific IgG antibody level to *Thermoactinomyces vulgaris* was 293 ng/mL (cut-off level 90 mg/mL).

This resulted in a diagnosis of hypersensitivity pneumonitis (HP) secondary to *Thermoactinomyces vulgaris* exposure. Since the disease presumably had an occupational origin, we reported the case to the Italian Workers' Compensation Authority (INAIL) for compensation, and recommended withdrawal from exposure to the contaminated environment.

Discussion

The main interest of this case is that the first examination by a specialist in occupational medicine was requested 27 years after the onset of symptoms. This was despite the clinical picture clearly indicating that the possible cause of the disease had to be sought in the workplace. It was probably the lack of adequate resources (in this case, of competence in occupational medicine) that delayed a thorough investigation (i.e., the search for precipitins) that should have been performed immediately, and prevented the completion of the diagnosis with the search and isolation of the etiologic agent in the working environment.

HP is an immunologically mediated lung disease resulting from repeated exposure to organic dusts or other environmental antigens (1, 9, 11). The original description of HP is attributed to Ramazzini (19), who in 1700 reported a lung disease in grain workers that was probably HP. Many anecdotal observations link this condition to a number of microbiological agents (8). Since there is no single radiologic, physiologic, or immunologic test specific for the diagnosis of HP, it often poses diagnostic challenges, even for expert clinicians (12). The prevalence of HP varies with the environmental risk factors, including antigen concentration, frequency and duration of exposure, antigen solubility, particle size, and the use of respiratory protection in the workplace. It has been re-

ported that up to 70% of exposed workers in contaminated office buildings develop HP (10).

HP was first associated with occupational exposure to contaminated humidifier or air-conditioning systems in office workers by Banaszak et al. in 1970 (2) *Thermoactinomyces vulgaris* is the most common humidifier organism to induce humidifier fever and allergic alveolitis (18, 25). In most cases, Thermophilic Actinomycetes have been isolated from the humidifier water or other reservoirs, and serum precipitating antibodies to these organisms were usually found in exposed subjects (6, 15).

In our case, we believe diagnosis is suggested by the classical case history (14, 20, 21), recurring symptoms related to occupational exposure, typical radiological pattern (17, 24) and detection of specific serum precipitins (5). According to recent studies, this clinical pattern (recurrent episodes of typical symptoms occurring 4-8 hours after exposure; weight loss; crackles; positive serum precipitins), even in the absence of a demonstrated offending agent, indicates at least a 62% probability of the presence of HP (12). Unfortunately, due to the lack of environmental tests the presence of *Thermoactinomyces* in the air conditioning system cannot be confirmed. Furthermore bronchoalveolar lavage (BAL) was not performed in the acute phase of the disease, when the finding of a lymphocytic alveolitis (lymphocytes accounting for more than 20% of total BAL cells) may help to understand the pathophysiology of the disease (22).

HP is a relatively common disease and it should always be considered in the differential diagnosis of febrile reactions and parenchymal lung diseases. Although the etiologies and clinical presentations have been well described, the diagnosis of HP is most often confirmed only after repeated bouts of acute manifestations or when irreversible damage to the lungs has already occurred. It has been observed that almost all cases were treated for a presumed infectious process or chronic bronchitis before the diagnosis was clearly established (3).

The diagnosis of HP is unlikely to be missed if the possibility of occupational or environmental causes is routinely considered in the differential diagnosis of any patients with a respiratory problem. A high index of suspicion and a careful environmental and occupational history are the keys to a diagnosis of HP (16). This case report points out the importance of an exhaustive occupational and environmental history which should be part of the clinical approach to every patient, not only in the occupational health setting, but also in primary care and in specialized secondary settings.

The environmental and occupational history should be obtained in a systematic manner to ensure that all relevant information is obtained. The history should include detailed information related to the work/home/leisure-time environment, the clinical course of the illness, focusing in particular on the relationship between environmental exposures and initial onset of the symptoms as well as timing of worsened symptoms in relation to work exposures or improvement away from work, and similar illnesses among fellow workers.

Probably, as a consequence of the lack of a correct environmental and occupational history, physicians repeatedly failed to prescribe immunological tests and environmental analyses to investigate exposure to specific pathogens.

Immunologic and environmental tests, however, seem to be necessary to confirm HP diagnosis and clarify the occupational/non-occupational etiology. In cases of allergic lung diseases it is important to detect the etiological agent in order to avoid or reduce further exposure and improve the clinical outcome of the disease. In particular, in cases of HP, it has been shown that avoidance of exposure prevents the disease from evolving to chronic interstitial lung disease with non-reversible lung fibrosis and respiratory failure (14).

Another possible explanation for the delay in the performance of diagnostic tests is that the physicians who treated the patient could have considered these tests too impractical. In fact, BAL is an invasive test; research of precipitins is not performed in all laboratories, so that the test had to be carried out in a laboratory 900 km from the patient's workplace. It is probably due to lack of resources (in this case, of easily available diagnostics) that the physicians reached only a generic diagnosis, without going into the cause of the disease. Making a broad symptomatic diagnosis of extrinsic bronchial asthma enables physicians to immediate-

ly start non-specific anti-inflammatory therapies, in particular steroid treatment, thus rapidly improving the patient's health. It seems to save time, trouble and expense for the patient since diagnostic procedures, such as precipitin testing, and environmental contaminants research, are not easily accessible within the local healthcare system and require long waiting times. Moreover, even though causing a delay in etiological diagnosis, an immediate start to treatment versus performing expensive tests may allow physicians to exert an implicit rationing of healthcare resources, an inevitable course of action in the current management of healthcare's limited resources. This crucial topic raises many ethical concerns and it is largely described in recently published works (7, 13, 26).

Even if oral corticosteroids remain the only effective drugs for HP, exposure withdrawal constitutes the ideal solution and, when it is possible, should definitely be the first step in the treatment approach. This requires further efforts on the essential role of looking for an etiological agent.

Pharmacotherapy as first line choice may hinder identification of the causative agent and thus obstruct primary prevention. Primary prevention is the goal of occupational medicine, but it should become the aim of all daily clinical practice which is often more concentrated on early diagnosis, secondary prevention and management of diseases, tertiary prevention.

Moreover, the lack of an identified etiological agent undoubtedly poses a significant obstacle to the recognition of the occupational origin of the disease, and subsequently to obtaining compensation. A recent editorial on asthma was entitled: "If you want to cure their asthma, ask about their job" (4). This phrase, which is strongly reminiscent of the teachings of Ramazzini, could be an interesting take-home message for all respiratory diseases, in particular for HP, for which an occupational or environmental cause can be detected and where primary prevention could prove highly efficacious.

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