SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2014; 31; 170-173

Metformin/glibenclamide-related interstitial lung disease: a case report

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Abstract. Interstitial lung disease (ILD) may be caused by a wide panel of recognized drugs. Despite the increasing number of reports in the literature, high-lightings of ILD related to oral hypoglycemic drugs are very infrequent. Herein, we describe the case of a 78-yr-old Caucasian diabetic woman who developed mild dyspnoea at rest, asthenia and fever while on treatment with oral metformin (2000 mg/day) and glibenclamide (12.5 mg/day). On hospital admission, pulmonary function testing (PFT), chest x-ray and thorax high resolution computed tomography (HRCT) were consistent with a diagnosis of ILD. The patient's clinical conditions significantly improved soon after the initiation of insulin therapy instead of oral anti-diabetics due to poor glycemic control. After excluding other known etiologies, the significant improvement in PFT along with the complete resolution of the radiologic findings in the absence of any additional therapeutic effort at 3 months suggested the causal link between previous oral hypoglycemic therapy and lung toxicity. Clinicians should always consider the role of drugs as causative agent in the diagnostic work-up of patients with suspected ILD. To our knowledge, this is the second report in the literature of a case of ILD related to the treatment with high doses of anti-diabetic drugs in a poorly controlled diabetic woman. *(Sarcoidosis Vasc Diffuse Lung Dis 2014; 31: 170-173)*

Key words: Interstitial lung disease; iatrogenic pneumonia; diabetes.

Introduction

It is well known that interstitial lung disease (ILD) can be related to a iatrogenic cause (1). The clinical presentation is variable (dyspnoea, dry cough) (2) and an inaccurate collection of the patient's history can lead to diagnostic and therapeutic mistakes. An increasing number of medications has been reported to cause side-effects affecting the respiratory system (3-7), but only a little is known about the lung toxicity of metformin in association with glibenclamide. In 1986 Klapholz L *et al* (8) described the case of a 56-yr-old woman affected by type II diabetes treated with glibenclamide (10 mg/day) and metformin (2550 mg/day) with bilateral pulmonary infiltrates at a chest X-ray and diffuse papulous skin lesions, histologically proven as leucocytoclastic vasculitis. The withdrawal of the oral hypoglycemic therapy, which was shifted to insulin therapy, and treating the patient with prednisone (0.5 mg/kg/day) led to a rapid resolution of the radiologic findings along with the improvement of the

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skin lesions in 10 days. Two weeks after the interruption of the corticosteroid therapy, metformin was reintroduced and, 2 days later, the patient showed a relapse of the dermatologic pathology. The Authors concluded that metformin, rather than glibenclamide, had an etiologic role in causing both the cutaneous lesions and the lung findings.

Case report

A 78-yr-old Caucasian non smoker woman was admitted to our Division referring a 3-month history of mild dyspnoea at rest, asthenia and fever. Her medical history was remarkable for the following conditions: arterial systemic hypertension, treated with carvedilol (12.5 mg/day) for 5 years, in combination with furosemide (50 mg/day) and ramipril (10 mg/day) for 4 years; ischemic heart disease, i.e. an acute heart attack episode occurred 4 years before, treated first with percutaneous transluminal coronary angioplasty (PTCA) and then, 7 months later, with aorto-coronary by-pass; chronic atrial fibrillation on oral anticoagulation treatment with warfarin for 3 years. Metabolic disorders included hypercholesterolemia, treated with atorvastatin (20 mg/day) for 3 years, and type II diabetes on therapy with an association of oral hypoglycemic drugs, whose dosage was increased in the last 3 months due to the poor control of glycemia levels (metformin from 1200 mg/day to 2000 mg/day and glibenclamide from 7.5 mg/day to 12.5 mg/day). The patient was a housewife with no domestic animals. Further exposure to environmental agents likely causing respiratory diseases was excluded after a careful interview. Allergy was ruled out as well. On admission, the patient was awake and alert, suffering from mild dyspnoea at rest. No further clinically significant signs were appreciated. Body temperature was 36.8°C. Atrial fibrillation was present with a heart rate estimated between 70-80 beats a minute, while blood pression was normal. The physical examination (i.e., auscultation) of the thorax revealed the presence of inspiratory bilateral crackles in the lower lung fields. Blood gases analysis was performed while the patient was breathing ambient air at rest. To date, arterial oxygen partial pressure (pO_2) was of 52.7 mmHg, carbon monoxide pressure (pCO_2) was of 37.2 mmHg with a PH of 7.45. Routine haematological and biochemical parameters were within the normal range. A mild anemia was instead appreciated along with increased serum levels of glucose and glycosylated haemoglobin (HbA1c) (12.1 %, normal range: 3.5-6 %). Searching for commonly tested auto-antibodies (Abs) (including rheumatoid factor, antinuclear, anti-citrullinated proteins, anti-DNA, anti-smooth muscle, anti-extractable nuclear antigens, anti-neutrophil cytoplasmic Abs) was negative. Serology for common respiratory viruses and bacterial intracellular pathogens (including RSV, CMV, EBV, Influenza viruses, Parvovirus B19, Chlamydia pneumoniae and Mycoplasma pneumoniae) was also negative. Pulmonary function testing (PFT) revealed a mild restrictive ventilatory pattern with a still preserved total lung capacity (TLC 4.16 L, 81.5 % of predicted). To date, the absolute value of forced vital capacity (FVC) was 1.67 L (63.5 % of predicted) as forced espiratory volume/1' sec (FEV_1) (1.67 L, 80.5 % of predicted) with an absolute Tiffeneau index of 100 %. The Hb-corrected single breath lung diffusion capacity of carbon monoxide ($DLCO_{sb}$) was moderately compromised (3.40 mmol/min/KPa; 49.7% of predicted). Standard chest X-ray showed bilateral infiltrates in the lower lung zones. High resolution computed tomography (HRCT) of the thorax revealed extensive and patchy ground glass opacities throughout the lung vertical axis with higher prevalence in the lower fields (cranio-caudal gradient). These findings were suggestive of alveolar involvement. Areas of normal pulmonary parenchyma were appreciated between ground glass opacities (Figure 1.A). Microbiological examination of three induced sputum samples collected on consecutive days was negative. Searching for malignant cells was also negative. Fiber-bronchoscopy and broncho-alveolar lavage (BAL) collection for further cytology, microbiology and immunology studies were not performed as the patient refused the exam. While the patient was under investigation, oral hypoglycemic therapy was suspended and insulin therapy was initiated to allow a better control of diabetes. The clinical conditions of the patient started to improve after the first 48 hours of insulin treatment. Repeated blood gas analysis showed an increase of pO_2 to 79.4 mmHg. The patient was discharged after 12 days of hospitalization with no indication of additional therapies and with a planned control visit at 3 months. In that occasion, the patient was no more symptomatic, chest physical examination was unremarkable and PFT were within the normal range, with Hb-corrected $DLCO_{sb}$ estimated at 6.13

mmol/min/KPa (90.1% of predicted). Routine haematological/biochemical parameters and blood gases analysis were also within the normal range. HRCT scan of the thorax showed a significant improvement with the almost complete resolution of the aforementioned alterations (Figure 1.B).

Discussion

Adverse effects of drugs on the respiratory system have become an important issue in pulmonary practice. Indeed, the list of medications causing ILD has expanded markedly over the past 30 years (1-7). However, to our knowledge very little is known about the causal relationship between oral hypoglycemic drugs and lung toxicity. Usually, drug-induced ILD develops after the patient has used the drug for a long period and symptoms improve once the drug is withdrawn. Cases of ILD have also been described after weeks or years after treatment termination.

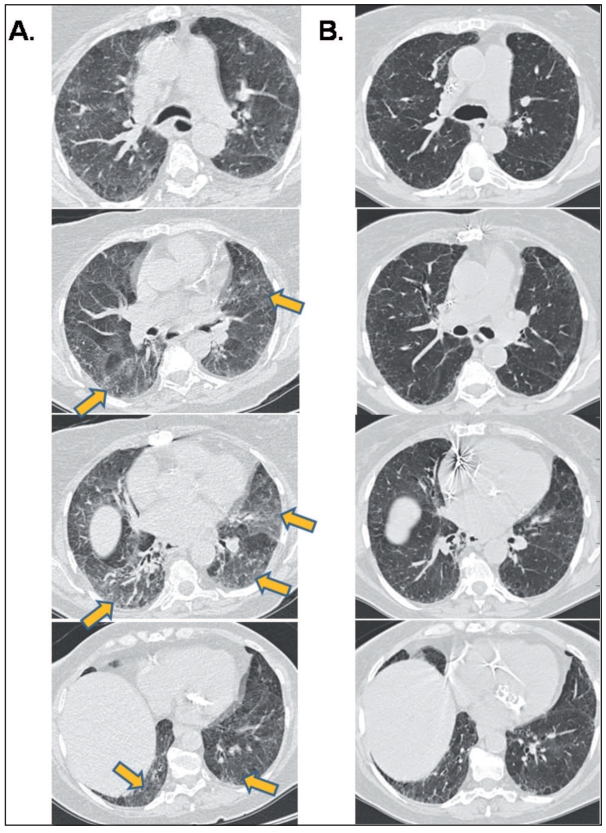

Fig. 1. Thorax HRCT performed on hospital admission revealed the presence of areas of heterogeneous and extensive increase in lung density, i.e.,ground glass opacities (arrows), through the vertical axis with higher prevalence in the lower lobes suggesting a fluid alveolar involvement (A). A marked improvement leading to the almost complete resolution of the imaging findings with no distortion of the interstitial architecture was appreciated after three months of stopping oral anti-diabetic therapy (B).

Herein we report the case of an elderly diabetic woman who developed progressive dyspnoea, fever and asthenia soon after increasing the dosage of metformin/glibenclamide due to the poor glycemia control. As symptoms were persisting over a 3-month period the patient was referred to our Division where thorax imaging revealed the presence of bilateral ground glass opacities in the lower lung fields. The clinical conditions of the patient improved significantly very shortly (2 days) after starting insulin therapy in spite of oral hypoglycemic drugs. Such an observation led us to hypothesize the existence of a causal link between the dose change of metformin/glibenclamide and the occurrence of lung disease. After excluding other known etiologies, the significant improvement in PFT along with the almost complete resolution of the radiologic findings in the absence of any additional therapeutic effort at 3 months further supported this belief.

A similar case was previously reported by Klapholz L *et al.* (8). As in our patient, clinical improvement was obtained after drug withdrawing but it was observed over a longer period (10 days). In addition, the use of corticosteroid therapy was needed. Finally, lung disease was not isolated as skin involvement was also present. As disease relapse occurred after metformin re-introduction the Authors definitely identified metformin as the causative agent. Unfortunately, in our case, in the absence of further literature evidence for comparison, it is quite difficult to argue to which extent the causative role has to be attributed to metformin or to glibenclamide.

Diabetes treatments have been related with either an increased or reduced risk of cancer. In a recent meta-analysis by Franciosi M *et al.* the use of metformin has not been associated with the risk of cancer and cancer-related mortality in diabetic patients (9). Conversely, as metformin also displays significant growth inhibitory and pro-apoptotic effects, its usage, alone or in combination with chemotherapeutic drugs, has been proposed for treatment purposes in several cancer models, including lung cancer (10). However, as epidemiological data have shown contrasting results in this issue, deciphering targeted molecular pathways is still under investigation.

Conclusions

To our knowledge, this is the second literature report of a case of ILD related to treatment with high doses of metformin/glibenclamide in a poorly controlled diabetic woman.

Clinicians should always be aware about the likely link occurring between lung pathology and drugs in the diagnostic work-up of ILD.

While liver and kidney drug-related side effects are routinely screened in clinical practice, less attention is paid to lung toxicity with under-diagnosis consequences, especially in elderly patients.

Informed consent

Written informed consent was obtained from the patient for publication of this report and of any accompanying images.

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