Int J Clin Exp Pathol 2016;9(2):1706-1712
www.ijcep.com /ISSN:1936-2625/IJCEP0018676

Original Article

Interstitial lung disease caused by psychiatric drug therapy

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Received October 28, 2015; Accepted December 25, 2015; Epub February 1, 2016; Published February 15, 2016

Abstract: With the discovery and development of mental disorders, the use of psychiatric drugs is increasing constantly. Besides the therapeutic effects, their adverse reactions (ADRs) are also found and continuously increased. Besides the most common adverse effects of psychiatric drugs reported so far, the reactions in the lungs may be another adverse effect, which may cause serious consequences and even be lethal if the patient continues to take the medicine. This paper described two cases of interstitial lung disease associated with psychiatric drugs, which were not reported in the previous literatures, case 1 is diagnosed with organizing pneumonia (OP) and nonspecific interstitial pneumonia (NSIP) induced by paroxetine, and case 2 is thought to be NSIP because of quetiapine administration, and in the meanwhile, we reviewed the possible mechanism of CYP polymorphisms.

Keywords: Psychiatric drugs, drug-induced interstitial lung disease, P450 enzymes

Introduction

With the clinical use of phenothiazine derivative chlorpromazine, the treatment of mental illness has accessed to the stage of modern medicine since the late 1950 s. The higher requirement of effective treatments of major psychiatric disorders such as depressive disorder or schizophrenia is needed because of their leading contributes to global disease burden over the past two decades [1]. The most commonly used pharmacologic therapies for psychiatric disorders are antipsychotic drugs, antimanic drugs, antidepressive drugs and antianxiety drugs. More and more psychiatric symptoms and patients are founded, while the etiology of psychiatry is still unknown, and the discontinuation rates of antidepressants (ADs) and antipsychotics (APs) increased gradually due to their ADRs [2]. ADRs of ADs and APs are common, with weight gain, metabolic dysregulation, sedation/somnolence, extrapyramidal motor symptoms (EPMS), sexual dysfunction, QT-interval prolongation and pneumonia among those observed most frequently [3-6]. Rarely, severe pulmonary drug toxicity associated with psychiatric drug therapy has been declared, only sporadic cases are occasionally reported in the literature [7-10]. Clinicians need to be aware of potential harms of interstitial lung disease (ILD) caused by psychiatric drugs.

ILD is one of four respiratory diseases, seriously affect people's health and quality of life, drug-induced interstitial lung disease (DILD) is one kind of ILD. Clinicians need to fully understand the drug toxicity and risk factors of patients, closely observe patients' clinical manifestations in the treatment. The major representatives of DILD include antimicrobial agents (e.g. nitrofurantoin), anti-inflammatory agents (e.g. methotrexate), biological agents (e.g. adalimumab), cardiovascular agents (e.g. amiodarone), chemotherapeutic agents (e.g. cyclophosphamide), and miscellaneous drugs (e.g. bromocriptine) [11]. Currently available evidence fails to confirm that all the psychiatric drugs have the adverse drug reaction of DILD, although few cases reports have been published, with simple causal relationship.

We describes two extremely rare cases of DILD due to psychiatric drug therapy, in order to warn clinicians to be aware of the potential risks for psychiatric drugs associated interstitial pneumonia, to make an early diagnosis and establish a proper treatment.

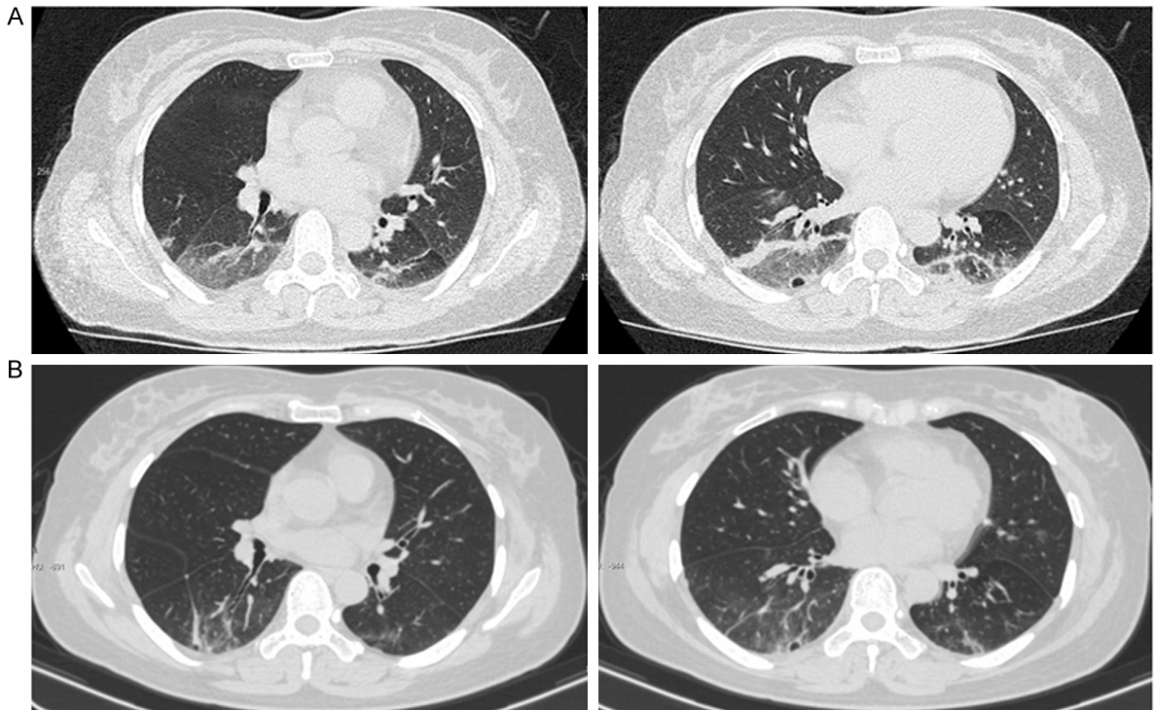

Figure 1. A. Computed chest tomography (CT) showed patchy dense consolidation and reversed halo sign in both lower lung zones. B. CT showed significant clearing of the infiltrates compared to the pictures before treating.

Case reports

Case 1

A 46-y-old woman presented with 5-month history of cough and blood tinged sputum with no known allergies, who was diagnosed with depressive disorder and insomnia and treated with olanzapine (10 mg/d) and clonazepam (2 mg, 3/d) for years. 6 months before her admission, the patient received a surgery for knee flexion deformity. Subsequently she developed a much more serious symptom of depression, and suffered from severe insomnia. Then the paroxetine treatment was added. Beside depression, the patient also had previous medical history of more than 10-year hysteromyoma. She had never smoked and drunk. She worked in a clothing factory, but had quitted 5 years before the admission. The patient became heavy with 15 kg weight gain in nearly a year. On physical examination, the patient had no fever, and blood pressure was 120/70 mmHg; pulse rate, 86 beats/min; and respiratory rate, 16 breaths/min. Auscultation detected fine rales in the lower zones of both lung fields. On the examination of limbs, the patient said right wrist pain occasionally. She had no other relevant findings.

The patient's laboratory tests were as follow: erythrocyte sedimentation rate (ESR), 21 mm in the first hour, blood routine test, coagulation, general biochemistry, c-reaction protein (CRP), immunoglobulins, autoantibodies, ANCA and tumor makers were all within normal ranges. Arterial blood gas analysis breathing room air (inspired oxygen fraction, 21%) showed a pH of 7.41, PaO_2 of 84 mmHg, PCO_2 of 38 mmHg, and bicarbonate concentration of 24.1 mmol/L. Sputum bacteriology and cytology gave no relevant findings.

Computed chest tomography (CT) showed patchy dense consolidation and reversed halo sign, a focal area of ground-glass opacity (GGO) surrounded by a more or less complete ring of consolidation in both lower lung zones (**Figure 1A**). Lung function tests showed a decreased diffusing capacity pattern: forced vital capacity (FVC) was 2.77 L (87.1%), forced expiratory volume in 1 second (FEV1) was 2.18 L/s (80.0%), total lung capacity was 3.92 L (77.8%), TLCOSB was 4.68 mmol/min/kPa (55.6%), RV/TLC-He 33.2% (95.9%). Subsequent bronchoscopy revealed no macroscopic abnormalities, and bronchoalveolar lavage fluid (BALF) culture had no positive results. The lavage fluid cell count

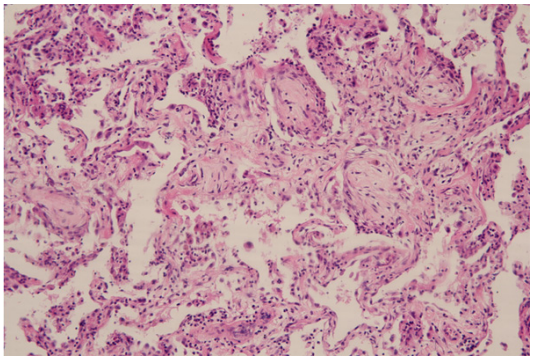

Figure 2. Hematoxylin-eosin stain showed lung tissue with a diffuse, mainly lymphocytic, interstitial infiltrate, with alveolar septal thickened; part of the alveolar cavity showed organization and aggregation of foam cell (×200).

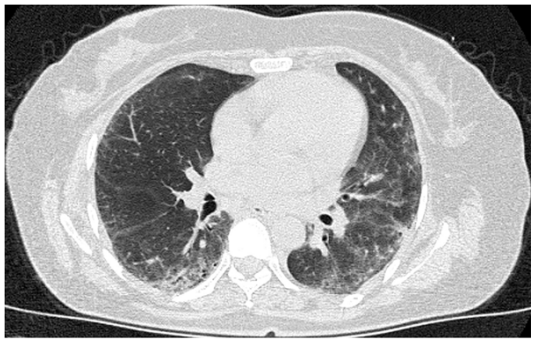

Figure 3. Showed diffuse patchy opacity and linear opacity.

showed 20.5% alveolar macrophages, 15.5% neutrophils and 64% lymphocytes, with CD3+CD4+/ CD3+CD8+ of 0.99. Thoracoscopic biopsies revealed interstitial pneumonitis: chronic inflammation of lung tissue, lung membrane thickening, with fibrous tissue hyperplasia and focal lymphocyte infiltration; alveolar septal was thickened with diffuse fibroplasia and lymphocyte infiltration; part of the alveolar cavity showed organization and aggregation of foam cell (**Figure 2**). The histopathologic features were consistent with NSIP and OP.

Considering the respiratory symptoms developed after the administration of paroxetine, DILD was suspected. Paroxetine was withdrawn, and she discharged from hospital and meanwhile she was treated with oral prednisone 24 mg for 2 weeks, and we tapered the dosage of prednisone during her follow up. Her chest radiograph showed significant clearing of the infiltrates (**Figure 1B**) and symptoms got prompt resolution.

Case 2

A 39-year-old woman was admitted to the hospital because of cough and sputum for 7 months. Despite the treatment with oral azithromycin for 2 months, her respiratory symptoms got no relief, then she had an X-ray in the outpatient, the chest radiography showed bronchovascular bundle thickened, and bilateral diffuse bronchopneumonic infiltrates, the doctor gave the treatment with intravenous cefuroxime and mucosolvan, but her symptoms had no significant improvement. So she was admitted for further evaluation.

The patient denied any allergies. She had medical history of anemia for years, which was treated with niferex, and she received a surgery of hysteromyomectory 7 years before her admission. In addition, the patient had a history of more than 10-year schizophrenia, and she was treated with various antipsychotic drugs, while no exact details were given, but what was important was that she changed the drug for quetiapine nearly 8 months before her admission.

Her vital signs were stable, with temperature of 36.6°C, blood pressure was 110/70 mmHg; pulse rate, 80 beats/min; and respiratory rate, 22 breaths/min. Auscultation revealed bilateral basilar crackles. Other examinations on physical were all negative.

The blood parameters were as follow: blood routine examination showed a hemoglobin of 90 g/L, hematocrit of 30.6%, mean corpuscular hemoglobin concentration (MCHC) of 294 g/L, mean corpuscular hemoglobin (MCH) of 22.4 pg, and white blood cell (WBC) count of 5460/mm^3 with a normal differential cell count. Serum iron was 4.4 μmol/L. Autoantibodies revealed antinuclear antibodies (ANA) positive, CRP, ESR, ANCA, coagulation, general biochemistry, and thyroid functions were all within normal ranges. Sputum cultures showed no pathogens. Arterial blood gas analysis breathing room air (inspired oxygen fraction, 21%) showed a pH of 7.41, PaO_2 of 118 mmHg, PCO_2 of 39 mmHg, and bicarbonate concentration of 24.7 mmol/L.

CT showed bilateral diffuse patchy opacity and linear opacity with subpleural dominancy (**Figure 3**). Lung function tests showed a mod-

Box 1. Criteria for diagnosis of drug reactions

Correct identification of the drug in question. Was the patient taking the drug? What dose? What duration?
Exclusion of other primary or secondary lung diseases
Temporal eligibility: appropriate latent period (exposure to toxicity)
Remission of symptoms with removal of challenge, recurrence with rechallenge
Singularity of drug; what other drugs was the patient taking?
Characteristic pattern of reaction to specific drug; previous documentation?
Quantification of drug levels that confirm abnormal levels (especially for over doses)
Degree of certainty of drug reaction: Causative; Probable; Possible

erate decreased restrictive capacity and severe diffusing capacity pattern: FVC was 1.96 L (58.2%), FEV1 was 1.90 L/s (65.5%), TLC was 2.93 L (58.2%), TLCOSB was 2.85 mmol/min/kPa (32.5%), RV/TLC-He was 37.09% (115.1%). Bronchoscopy showed no apparent changes, and BALF culture revealed no pathogen. The lavage fluid cell count showed 79% alveolar macrophages, 5% lymphocytes, 15% neutrophils, and 1% eosinophils, with CD3+CD4+/CD3+CD8+ of 1.17. The patient refused thoracoscopic biopsy and even transbronchial lung biopsy.

Although there was lack of histopathologic results, we suspected the patient was DILD associated with quetiapine, because the respiratory symptoms developed after the treatment of quetiapien, and the CT features corresponded with NSIP, which was one kind of manifestations of DILD. So we suggested her see a doctor in mental hospital, and change another antipsychotic drug instead of quetiapine, under the guidance of a professional psychiatrist, in case of withdraw reaction of quetiapine and psychic seizure. And then accepted the treatment of oral corticosteroids. 6 months after her discharge, we followed up through telephone, the patient had stopped taking quetiapine and methylprednisolone, and her symptoms were relieved. But she refused the CT re-examination.

Discussion

Different person responds differently to the drug therapy, with the same diagnosis and treated with the same medication, most patients react well, some of the patients have no response, and others may react with adverse reactions with or without therapeutic effects. The lungs are always a target for the drugs because of their large contact surface and their metabolic function. The ADRs perform in the lungs are called drug-induced lung injury; the most common form is DILD. The person-to-person variability of a drug response makes the diagnosis difficult. It is also clinically challenging when people have different kinds of drugs. Whether it's ADR of a certain drug or it's the interaction of different drugs also makes clinicians confused. The diagnosis of DILD is some kind of exclusion; Irey [12] defined a set of criteria for the diagnosis of drug reactions (**Box 1**). The major representatives of DILD include cytotoxic, cardiovascular, antimicrobial, biological agents and miscellaneous drugs [11], rarely literatures reported psychiatric drugs associated DILD. Herein, we reported two cases of DILD, respectively induced by paroxetine and quetiapine, and we searched literatures through PubMed, only sporadic cases about DILD related to psychiatric drugs, especially ADs and APs, are reported [13-16].

The variability in drug response among patients is multifactorial, including extrinsic factors like environmental aspects and also genetic and intrinsic factors that affect the disposition of a certain drug, with inheritance as a determinant one [11, 17]. Patients respond individual variably to drugs due to different pharmacogenetics and pharmacodynamics, while many drugs are metabolized by P450 (CYP) enzymes, including most psychiatric drugs. Polymorphisms in CYP enzymes are substantial in the individual variability in metabolic capacity. In psychiatry, CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 are the most relevant CYP enzymes, especially CYP2D6 with over 80 allelic variants described so far [18]. CYP2D6 is the first drug metabolizing enzyme reported to be polymorphic, and is the most studied related to drug metabolism. It is also declared to be related to the ADRs of psychiatric drugs, like antipsychotic-induced extrapyramidal syndromes [19]. The CYP enzymes are predominantly found in the liver, and they are also found in many other tis-

sues, including the lungs, and is CYP2D6 [20]. So for many drugs, especially for psychiatric drugs, the lungs also act as a metabolism site, and drugs can induce specific respiratory reactions.

Paroxetine is a potent selective serotonin reuptake inhibitor (SSRI) antidepressant drug gets rid of many of the side effects compared with the old tricylic antidepressant drugs (TCAs). The most commonly observed ADRs of paroxetine were nausea and somnolence, sweating, tremor, dizziness, insomnia, sexual dysfunction, and bleeding problems [21]. The ADRs of lung injury of paroxetine rarely reported, besides our report (case 1), Antonello et al [13] reported a case report of diffuse alveolar damage caused by paroxetine. First-pass metabolism of paroxetine is metabolized by both CYP2D6 and CYP3A4, and metabolism of paroxetine is heavily affected by its high plasma protein binding and its CYP profile. SSRIs are also inhibitors of CYP2D6, including paroxetine. Therefore the administration of these SSRIs to a patient taking other drugs that also metabolized by the same CYP profile may cause a shift in plasma concentrations, which potently leads to an adverse effect. In our report, the patient also took olanzapine and clonazepam for years apart from paroxetine, therein, olanzapine was metabolized by CYPIA2 and CYP2D6. It is clinically challenging to distinguish whether it was the ADR of paroxetine or the interaction between olanzapine and paroxetine. Anyway, the respiratory symptoms developed after the administration of paroxetine, and the clinical symptoms relieved and the infiltrates in CT significant absorbed after the withdrawn of the drug and the corticosteroid therapy. Other SSRIs such as fluoxetine [22, 23] and venlafaxine [14, 24] associated DILD were also published in some case reports.

In case 2, although we lacked of histopathologic evidence, but our therapy was succeeded because of the improvement of respiratory symptoms. Quetiapine is an atypical antipsychotic medication used extensively for treating schizophrenia, bipolar disorder, and major depressive disorder. In addition to our report (case 2), Morikawa et al [25] described one with recurrence of an abnormal shadow was seen when quetiapine was reintroduced, and Kim et al [16] published another case of DILD related to quetiapine. Quetiapine is mainly metabolized by CYP3A4 and CYP2D6, like other APs, metabolism of quetiapine is largely influenced by CYP2D6. Other APs like clozapine [26], sertraline and risperidone [27] were also occasionally seen in the literatures.

Wijnen et al indicated that DILD appeared to be related to polymorphisms of at least one CYP [28]. Jan van der Weide et al [18] indicated that CYP polymorphisms apparently influenced the disposition of psychiatric drugs, especially ADs and APs, which was responsible for the development of a significant number of adverse drug reactions. Wijnen et al [29] again reviewed the relationship between DILD and CYP polymorphisms, revealed that CYP polymorphisms presented substantial host susceptibility risk for the development of DILD. Currently more than 100 kinds of drugs have been recommended for genetic testing according to drug specifications approved by the Food and Drug Administration (FDA), including 32 kinds of psychiatric drugs, including tricyclic antidepressant drugs, antiepileptic drugs, SSRIs and antipsychotic drugs [30]. CYP2D6 is the main metabolic enzyme for psychiatric drugs, and the dysfunction of the enzyme may result in toxic serum levels, and then further lead to severe side effects. The ADRs of psychiatric drugs in the lungs also include pulmonary embolism, pneumonia [13, 31-33], and persistent pulmonary hypertension [21], but the most common form is DILD.

Consequentially, it is important to be aware of the potential risk for DILD associated with psychiatric drugs (especially ADs and APs) therapy, whether its ADR of a certain drug or the interactions among drugs, and maybe it is better to perform CYP genotyping according to psychiatric drugs metabolic enzyme to evaluate the safety of the drugs before use it.

Disclosure of conflict of interest

None.

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