An atypical case of drug-induced lupus syndrome

Abstract

DIL is an autoimmune vasculitis against certain drugs that lead to autoantibodies in some patients causing a clinical syndrome with similar clinical manifestations of SLE. A 30 year old female was admitted for dry cough, polyarthralgia, and subfebrile fever that arouse three weeks after termination of antibiotic treatment for maxillary sinusitis. Computed tomography revealed multiple subpleural nodules. BAL culture was negative for bacteria, fungus, and ARB. Histopathologic examination of the TBB specimen revealed granulomatous inflammation. ANA, P-ANCA, MPO-ANCA, PR3-ANCA was positive while anti-ds-DNA, C-ANCA, C3 and C4 were negative. Anti-histone antibody was high. Symptoms resolved within three months after methylprednisolone treatment. Final diagnosis was DIL due to amoxicillin clavulanate.

DIL is now a diagnostic challenge due to its atypical presentation with significant overlap of the clinical and laboratory findings.

Keywords: drug-induced lupus, SLE, DIL, drug-induced vasculitis, lupus-like syndrome, amoxicillin-clavulanate

Introduction

Certain drugs may trigger an autoimmune response that induce autoantibodies which may cause a clinical syndrome with features similar to systemic lupus erythematosus in some patients, termed drug-induced lupus. These adverse reactions include fever, rash, leucopenia, arthritis, vasculitis, pulmonary manifestations, and symptoms of SLE [Systemic Lupus Erythematosus (SLE)]. DIL [Drug-Induced Lupus (DIL)] although akin to SLE reveals notable differences in clinical and autoimmune features.1,2 Pulmonary complications like interstitial pneumonia, adult respiratory distress-like syndrome, and pleural effusion are extremely rare.3-5 DIL is now well established and many other autoimmune disorders including vasculitis may arise as a drug reaction. Most of the cases of antibiotic induced autoimmune phenomena are due to vasculitis. Mortality rate of DIL is low and prognosis is excellent once the drug is discontinued although rare significant complications may come out due to systemic manifestations. The rate of acetylation is genetically predetermined and subjects with slow acetylation rates have a higher incidence of DIL.6,7 Acetylation rate is the hallmark of DIL that determines the prognostic outcome or the severity of the clinical profile.

We present the case of a patient who developed subfebrile fever, subpleural nodules, and mediastinal lymph node enlargement following amoxicillin-clavulanate treatment. There are fundamental differences in the clinical features of DIL and vasculitis that may allow an accurate diagnosis in most of the patients but the distinction was not easily achievable in our case due to the significant overlap of clinical and laboratory manifestations with an atypical clinical profile. The clinicians should be aware of the variable and atypical clinical profile of DIL that may cause a diagnostic confusion leading to a severe prognostic outcome if the offending agent is not withdrawn promptly.

Case report

A 30 year old woman was admitted for dry cough, polyarthralgia, and subfebrile fever that developed following two weeks of amoxicillin-clavulanate treatment for maxillary sinusitis. Her past medical history was remarkable. The family history did not reveal any disease of medical interest. Four weeks before admission the patient developed fever (38.4°C), postnasal purulent discharge, and maxillary pain. WBC was 13.2×10³/ml with 79 percent neutrophils, CRP: 55.5, ERS: 48mm/h. The patient was commenced on amoxicillin clavulanate 1000mg bid for fourteen days. Dry cough, dyspnea on exertion, polyarthralgia, and fever occurred three weeks after amoxicillin clavulanate treatment. Chest x-ray was normal (Figure 1). Blood biochemistry was within normal limits. There was no radiologic abnormality on joint films. Arterial blood gases; pH: 7.39, pO₂: 84.2, and pCO₂: 38.6mm Hg. ECG revealed sinus rhythm (84/min). Tuberculin test was negative. Chest CT showed bilateral multiple subpleural nodules in the lingula (one; 3mm), left lower lobe (multiple; 1-2mm), right lobe anterior segment (two; 5mm and 15X10mm) (Figure 2). Serum ACE was 24U/L. Sputum smear and culture were negative for bacteria, mycobacteria, and fungi.

Figure 1 Normal initial chest x-ray.
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maxillary sinusitis revealing overlapping manifestations of DIL and
findings. We present a case that presented with an atypical clinical

Symptoms, laboratory, and radiologic findings completely resolved
within three months of steroid treatment. The patient showed an
uneventful recovery following six months of steroid treatment.

Discussion

It has long been known that many drugs, including antibiotics
can induce DIL or vasculitis.2,3 Patients can be designated as DIL or
vasculitis according to the accepted definitions, clinical, and serological
pictures. We present a case that presented with an atypical clinical
picture of vasculitis following amoxicillin-clavunate treatment for
maxillary sinusitis revealing overlapping manifestations of DIL and
vasculitis4,5 due to amoxicillin-clavunate. The final diagnosis was
DIL due to positive anti-histone antibody. After steroid treatment, the
patient showed an outstanding outcome with resolution of symptoms,
clinical, laboratory, and radiologic findings. The patient was a
diagnostic challenge for the clinician because the risk of developing
DIL with amoxicillin-clavunate is extremely rare.4,5 Moreover, the
distinction between DIL and vasculitis was not achievable due to the
the significant overlap of the clinical manifestations between these two
techniques in our case. DIL patients present with various manifestations

like arthralgia, pericarditis, pleuritis, and fever. Dry cough, subfebrile
fever, and polyarthralgia were the predominant symptoms in our case.

Chest CT revealed pulmonary nodules and enlarged mediastinal lymph
nodes that are unusual in DIL. And thirdly, the clinical manifestations
were atypical for DIL. Notably the presence of subpleural nodules and
the enlarged mediastinal lymph nodes identified by chest CT lead to
diagnostic confusion.

Aloush has reported crucial differences between the DIL and
ANCA-associated vasculitis by reviewing their likeness and
discrepancies. DIL patients have more musculoskeletal complaints,
more serositis, and gastrointestinal involvement while the ANCA-
associated vasculitis more frequently presents with pulmonary and
renal involvement. ANA, anti-DNA, and anti-histone antibodies
are prevalent in DIL, p-ANCA is found in a similar proportion
of patients in both groups whereas c-ANCA is detected only in
patients with vasculitis. DIL patients usually recover completely
after drug withdrawal while patients with vasculitis need steroids or
immunosuppressive drugs frequently.4 Steroid treatment was needed
because of the persistent clinical profile of our patient. There was
also significant overlap of laboratory findings of DIL and vasculitis
in this case. Antinuclear antibodies are positive in over 50% of cases
and native anti-DNA is reported.5 These markers were negative.
Resolution of symptoms, positive serum anti-histone antibody with
positive c-ANCA, and complete resolution radiologic findings
after drug withdrawal strongly suggested DIL due to amoxicillin-
clavunate treatment.

Some patients with DIL develop a much more serious picture
of adverse autoimmune response characterized by high titres of
antibodies to MPO with clinical manifestations including pauci-
immune necrotizing and crescentic glomerulonephritis, upper
respiratory tract disease, and pulmonary hemorrhage with negative
or low titres of ANA.10,11 There were no signs of MPO-ANCA
vasculitis with alveolar hemorrhage and microhematuria supporting
the presence of alveolar and glomerular inflammation as Bosch has
suggested.12,13 DIL usually occurs in a few weeks of treatment but
may develop after months or years. It is not usually dose dependent
and frequently improves after drug withdrawal.1,5,7 The symptoms
appeared two weeks after antibiotic treatment was completed in
our patient. Antibodies to double-stranded DNA were absent and
complement levels were normal. The PR3-ANCA and MPO-ANCA
serum levels decreased in correlation with the course of symptoms
and the resolution of radiologic findings after antibiotic treatment.

The pathogenesis of drug-induced lupus is uncertain. However,
many different theories exist for the pathogenesis of drug-induced
lupus.2 The predominant pathogenetic mechanisms that influence
the risk of DIL occurrence are genetic differences in drug metabolism
such as the acetylator status and the immunogenetic characteristics
of the patient. Possible genetic risk factors include human leukocyte antigen
(HLA)-DR4, HLA-DR0301, and the complement C4 null allele. These
factors vary between different agents.14-16 The mechanism responsible
for ANCA and vasculitis in patients on amoxicillin clavunate is
unknown. ANCA production may occur due to the interaction
between amoxicillin clavunate and neutrophils or neutrophil MPO.
The reactive intermediates that are activated by MPO and hydrogen
peroxide are immunogenic for T-cells and stimulate the immune
system.17,18 The cytotoxic activity of the metabolites determine the cell
death and production of autoantibodies.19 Vasculitic symptoms were
not present in our case but systemic manifestations required steroid

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treatment. The amoxicillin clavulanate associated vasculitis or DIL is rare. It is important to be aware of this complication because early withdrawal of the drug results in clinical recovery and may prevent a fatal outcome. Early recognition of this syndrome is an extremely important point because prompt drug withdrawal eventuates in clinical recovery and prevents severe complications.

Respiratory and systemic manifestations were preliminary in our patient. The clinical findings and the serologic markers were inadequate for exact DIL, ANCA-associated vasculitis or collagen vascular disease diagnosis. Resolution of symptoms together with normalization thelung nodules and the enlarged mediastinal lymph nodes after steroid treatment strongly suggests drug induced autoimmune disease. Genetic factors, immunogenetics, acetylator status, DNA methyltransferase activity, and autoantibodies including antinuclear, anti-histone, and antineutrophil cytoplasmic antibodies may play a role in the pathogenesis of DIL.6–12 The complex pathogenetic mechanism of DIL leads to a variable patient profile concerning the symptoms, laboratory, and radiologic manifestations. Consequently, different presentations, overlap syndromes, atypical clinical, and laboratory findings associated with drug-induced disease represent a diagnostic challenge for the pulmonary clinician. The current case does not fit into any of the previously designated classifications.

Conclusion

The pathogenetic mechanisms of DIL remain uncertain and may lead to variable manifestations between different drugs. Patient characteristics may influence risk of DIL and define the clinical profile including the laboratory and the radiologic findings. Genetic factors, immunogenetics, acetylator status, DNA methyltransferase activity, and different autoantibodies lead to a complex pathogenetic DIL pattern. This complex pathogenetic mechanism is predominantly liable for the diversity of the patient’s clinical profile. Our patient presented with atypical clinical manifestations, laboratory, and radiologic findings that were neither compatible with DIL nor with vasculitis. The only clue to DIL diagnosis was the high serum antihistone level. Clinicians should bear in mind that the identification of DIL and distinction from vasculitis may not be easily achievable due to the atypical patient symptoms, overlapping clinical, and laboratory manifestations. Consequently, we believe that drug-induced vasculitis would be a better term to designate drug-induced lupus like vasculitic or autoimmune disorders.

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None.

Conflict of interest

Cuneyt Tetikkurt, Seza Tetikkurt do not have any conflicts of interests to declare associated with this case report.

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