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CASE REPORT

Case report of chronic cough in primary care: a diagnostic challenge and lessons to learn

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Abstract

Cough is one of the most common complaints seen at the outpatient primary health clinic. While the most common aetiologies of chronic cough are asthma, chronic obstructive pulmonary disease, postnasal drip, gastroesophageal reflux disease, drug-induced, and tuberculosis, we often overlook that chronic cough, especially in a young female, can be the initial presenting complaint of an autoimmune disease. In this case report, we present a case of 35-year-old woman with no known prior medical illness who presented with chronic cough for 1 year with no other symptoms initially; but later in the disease course, the patient complained of multiple, symmetrical small joint pain, which led us to the diagnosis of seronegative rheumatoid arthritis.

Introduction

Rheumatoid arthritis (RA) is a systemic, inflammatory disease primarily affecting synovial joints with possible involvement of other organs; and the lungs are a common site of extra-articular disease.[1] Extra-articular involvement occurs in about 40% of patients with RA and includes vasculitis, skin and visceral nodules, Sjögren's syndrome, pulmonary fibrosis, and anaemia of chronic disease.[2] Successful management of systemic manifestations of RA is dependent upon control of the underlying joint disease and this includes the use of a glucocorticoids, immunosuppressive agents, and biologic therapies.[2]

According to the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA, patients who score ≥6/10 are diagnosed as definite RA[3]; those who score <6/10 are not classified as having RA and should be reassessed in the future.[4]

Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) are the antibodies that define a patient with seropositive RA. However, 15–25% of RA can be seronegative, meaning that these patients lack RF and anti-CCP antibodies.[5]

Clinical features suggestive of RA (i.e., elevated inflammatory markers and a significant and sustained response to a trial of prednisolone) may indicate the diagnosis of RA.[5]

The 2010 diagnostic criteria emphasise early identification of patients with RA and early treatment to improve outcomes. However, the diagnosis of RA becomes more difficult in patients with an uncommon presentation in early stages of the disease. It is interesting to note that the patient in this case report initially presented with a lung complication of RA instead of the typical symmetrical polyarthritis.

Case presentation

A 35-year-old housewife presented initially to the primary health care clinic with a chief complaint of dry cough for the past 3 weeks. She had no known medical illness and was a non-smoker. There was no frequent nasal discharge, congestion, itchiness, or sneezing to suggest allergic rhinitis, no episodic wheezing or dyspnoea to suggest bronchial asthma, no heartburn to suggest gastro-oesophageal reflux disease (GERD), and no weight loss or night sweats to suggest pulmonary tuberculosis (PTB). Fine crepitations were noted over the right lower zone upon auscultation, and sputum acid-fast bacilli (AFB) and a chest x-ray (CXR) were ordered to rule out PTB, as it is the most common cause of prolonged cough. She was given oral amoxicillin/clavulanic 625 mg twice daily for 1 week to cover for community-acquired pneumonia. During subsequent visits, the patient's cough persisted but PTB workup was negative; a chest x-ray from April 2019 showed reticular opacities over the right lower zone and no

air bronchogram. The patient was prescribed a 3-day course of oral azithromycin 500 mg once daily to cover for atypical pneumonia.

After 5 months, the patient presented again to the primary health clinic with persistent cough. The cough was dry, not aggravated or triggered by environmental factors like cold or dust and was not relieved with antitussive medication. A revisit of the history revealed that the patient had a history of working in an electronics and plastics factory for 1 year (2006–2007). The patient also had a family history of bronchial asthma and was a passive smoker. Given the history, the possibility of obstructive airway disease as the cause of chronic cough was considered, and patient was given a trial of bronchodilator (2 puffs MDI salbutamol, as needed). However, no baseline spirometry or peak expiratory flow rate (PEFR) was performed before or during the bronchodilator use. On a subsequent visit 1 month later, the patient continued to complain of a dry cough despite daily use of the bronchodilator.

Another PTB workup was completed: sputum AFB was negative, but the Mantoux test showed 10 mm induration. Repeated chest x-ray showed progression of the interstitial opacity involving the bilateral lower zones. The patient had a history of contact with a PTB patient 3 years prior. A diagnosis of latent PTB was made for this patient based on a persistent cough and positive Mantoux test with a history of PTB contact. She was treated for latent PTB and completed a 6-month course of daily oral isoniazid 300 mg and daily oral pyridoxine 10 mg.

The patient continued to complain of unresolved cough 8 months after the onset of symptoms; the cough was now associated with generalised body ache for 1 month. No significant findings were noted upon examination. Chest x-ray revealed fibrotic changes in the lungs and the case was referred to a chest physician for an opinion and a spirometry test and high-resolution computed tomography (HRCT) scan were arranged. While waiting the appointment, the patient received symptomatic treatment for the cough and body ache.

The patient presented 4 months later with persistent cough, shortness of breath, and pain over multiple bilateral small joints in her hands, wrists, and right ankle. The small joint pain was associated with early morning stiffness bilaterally over the hands and wrists that lasted for >30 minutes each day. In addition, she had experienced significant weight loss of approximately 10 kg over 1 year. X-rays of both hands showed periarticular osteopenia. ECG showed no significant pathology. The lung function test showed restrictive lung disease: FVC 68% and FEV1/FVC 91%. The HRCT scan showed nonspecific interstitial pneumonia (NSIP). Based on these findings, she was screened for connective tissue disease. The results were as follows: RF and anti-CCP were both negative, ANA was positive (1:640), dsDNA was negative, C3 and C4 levels were normal, CRP was 37.8 mg/L, ESR was 51mm/hour, and haemoglobin (Hb) was 13.8 g/dL. All other baseline investigations were normal.

The case was referred to a rheumatologist and was treated as seronegative RA. The patient was initially treated with prednisolone, methotrexate (MTX), sulfasalazine, and interarticular triamcinolone in the wrists bilaterally and the right ankle. The sulfasalazine was stopped after 10 months of treatment as the patient continued to complain of joint pain after optimising the medication, which was later changed to cyclosporin. During subsequent follow-up, the patient continued to complain of chronic cough but reported improvement compared with the cough before treatment, and the joint pain had improved after the cyclosporin was initiated. The patient is currently being followed up by primary health care and the rheumatology clinic.

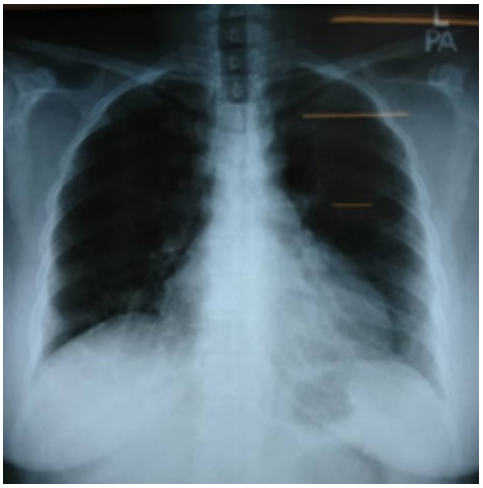

Figure 1. Chest x-ray (CXR) from April 2, 2019.

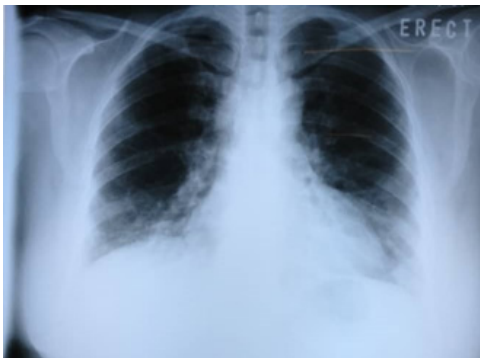

Figure 2. CXR from November 18, 2019.

Discussion

This case has taught us several lessons that we think may be beneficial to share with other primary health care doctors. It also highlights a few lessons in patient management that led to a 1-year delay in diagnosing a young female with chronic cough.

The first lesson is that this patient was initially treated for bronchial asthma and was given a bronchodilator for 6 months. Asthma is a clinical diagnosis; based on the Global Initiative of Asthma (GINA) 2021, a symptom pattern suggestive of asthma and airflow limitation on initial spirometry that completely reverses to normal following bronchodilator administration confirms the diagnosis of asthma.[6] An isolated cough with no other respiratory symptoms or chronic production of sputum decreases the likelihood that the respiratory symptoms are due to asthma.[6] As in this case, family history alone is not enough to diagnose asthma without the presence of clinical signs and symptoms. Therefore, it is important to refer a case with chronic cough for spirometry evaluation if there is any doubt regarding the diagnosis. The use of bronchodilator is justified in a case that is strongly suspected to be asthma where spirometry is not accessible to review the reversibility of the airway narrowing with a bronchodilator. However, in this case, the use of a bronchodilator to treat the cough was inappropriate, as the patient did not have the characteristic symptoms of bronchial asthma. This practice should be avoided in the future as it unnecessarily exposes the patient to side effects of bronchodilator use. An early lung function test should have been arranged to assess pattern of airflow limitation before initiating any treatment.

The second lesson is that the patient was also treated for latent pulmonary tuberculosis (LTBI). LTBI is defined as infection with *Mycobacterium tuberculosis* complex in which the bacteria may be alive but in a state of dormancy and not causing any active disease or symptoms.[7] LTBI is diagnosed based on the following criteria: 1) no symptoms to suggest active disease, 2) normal CXR/static CXR findings, 3) smear/culture negativity for *M. tuberculosis* from sputum or bronchoalveolar lavage, and 4) positive TST (i.e., Mantoux test).[7] In Malaysia, a TST ≥10 mm is considered positive for LTBI for most individuals; however, LTBI screening should only be performed on high-risk individuals: 1) HIV-infected persons, 2) organ transplant recipients, 3) persons receiving immunosuppressant drugs, 4) recent close contacts with TB(<2 years), 5) recent immigrants (<2 years) from high prevalence countries, 6) intravenous drug users, 7) residents and employees of high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, hospitals, and other health care facilities), and 8) persons with fibrotic changes on CXR consistent with old TB (patients with calcified lesions should be excluded).7 In this case report, the patient had contact with a tuberculous patient 3 years prior. The patient also presented with a chronic cough that did not resolve with antibiotic treatment, had weight loss, and her x-ray showed bilateral lower zone interstitial opacity that warranted the treating doctor to initiate workup for TB. Repeated TB workup was done as the patient's symptoms were not improving with antibiotics, and the repeated CXR showed progressive changes. Sputum AFB was negative. Diagnosis of LTBI in this patient was made based on a history of contact with a PTB patient, persistent cough, and positive Mantoux test; however, it is contradicted by the CXR findings that showed progressive changes, which warranted further expert referral to confirm the definite aetiology of the chronic cough in this patient.

HRCT showed NSIP in this patient. In general, interstitial lung disease (ILD) is categorised into cases that are associated with known causes and those that are idiopathic. The most common causes of ILD are exposure to occupational or environmental agents, drugs, and radiation.[8] The two most common causes of idiopathic interstitial pneumonia (IIP) are idiopathic pulmonary fibrosis (usual interstitial pneumonia [UIP]) and NSIP.[9] Idiopathic pulmonary fibrosis typically presents with insidious onset of dyspnoea and non-productive cough over several months in a patient over 60 years old with features of UIP on HRCT.[10] NSIP can be idiopathic or associated with HIV infection, drugs, connective tissue disease, and hypersensitivity pneumonia.[11] In a young female, autoimmune disease should be considered as a differential diagnosis. The

differential diagnosis of NSIP in connective tissue diseases is systemic lupus erythematosus (SLE), Sjögren's syndrome, and systemic sclerosis; NSIP can be present in RA but is less common than UIP.[11] Furthermore, this patient did not have features of SLE, such as butterfly rash, oral ulcers, alopecia, or systemic sclerosis features, such as skin thickening and hardening over fingers, hands, and face, digital tip ulcers, or Raynaud's phenomenon.

Some patients with IIP have features that suggest underlying autoimmune diseases but do not meet the established criteria for a connective tissue disease. This is the most likely explanation for the chronic cough in this patient. This condition is termed 'interstitial pneumonia with autoimmune features' (IPAF).[12]

Table 1. Classification criteria for IPAF.[12]

1. Presence of interstitial pneumonia (by HRCT or surgical lung biopsy) *and*,
2. Exclusion of alternative aetiologies *and*,
3. Does not meet criteria of a defined connective tissue disease *and*,
4. At least one feature from at least two of these domains:
   A. Clinical domain
   B. Serologic domain
   C. Morphologic domain

A. Clinical domain:
Distal digital fissuring or tip ulceration, inflammatory arthritis or polyarticular morning joint stiffness ≥60 min, palmar telangiectasia, Raynaud's phenomenon, unexplained digital oedema and Gottron's sign

B. Serologic domain:
ANA titre ≥1:320 with diffuse, speckled, or homogenous patterns; ANA of any titre with a nucleolar pattern; ANA of any titre with centromere pattern, rheumatoid factor ≥2× upper limit of normal, anti-CCP, anti-dsDNA, anti-RO, anti-LA, anti-ribonucleoprotein, anti-Smith, anti-topoisomerase, anti-Trna synthetase, anti-PM-Scl, anti-MDA-5

C. Morphologic domain:
HRCT appearance suggestive of NSIP or other IIP, histologic patterns or features of NSIP or another IIP, multicompartment involvement such as unexplained pleural effusion or thickening, unexplained pericardial effusion or thickening, and unexplained intrinsic airways disease

The importance of this case report is in highlighting a case with a diagnostic challenge in primary health care and lessons that we can learn to improve patient management in the future. As primary health care providers, we must be thorough in our clinical assessment and detailed in history taking so that we do not overlook any important information that could help us to obtain a correct diagnosis and ensure optimal management for the patient. Multidisciplinary involvement, such as with a family medicine specialist, respiratory physician, rheumatologist, or radiologist, is important in the management of certain cases, especially those that present with atypical symptoms and are not straightforward.

Conclusion

This case is an example of how a common complaint like chronic cough leads to a delay in diagnosis if not investigated or managed properly. Autoimmune disease should always be a differential diagnosis in any young female presenting with chronic cough in primary care.

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Conflicts of interest

The authors declare there are no conflicts of interest relevant to this article.

Patients' consent for the use of images and content for publication

Informed consent was obtained before preparation of the case report.

What is new in this case report compared to the previous literature?

- This case report highlights an example of a case that presented in an atypical way that misled the attending doctor in diagnosis and delayed appropriate management of a young female with chronic cough. These lessons may be beneficial to other primary health care doctors to avoid making the same mistakes.
- This case report highlights how the most common complaints in primary health clinics can represent an atypical initial presentation of a certain disease. This case encourages the treating physician to search vigilantly for clues to come to a correct diagnosis.

What is the implication to patients?

A proper assessment of the cough would have avoided initiation of unnecessary treatment, such as bronchodilators or LTBI treatment. Obtaining a correct diagnosis will ensures appropriate management of her symptoms.

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