CASE REPORT

Leflunomide-induced chronic cough in a rheumatoid arthritis patient with pulmonary tuberculosis

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SUMMARY

A 40-year-old lady presented with clinicoradiological features suggestive of pulmonary tuberculosis, which was confirmed on sputum smear examination, and was started on four-drug antitubercular treatment. On subsequent visits, she complained of persistent cough, despite improvement in other symptoms. A careful anamnesis revealed that the patient had been taking leflunomide for rheumatoid arthritis for the last 10 years, and this was suspected to be the cause of the cough. The patient became asymptomatic upon stopping the drug, thereby confirming the hypothesis.

BACKGROUND

Leflunomide (LFM) is one of the disease-modifying antirheumatic drugs. The long-term use of LFM affects multiple systems. The respiratory side effects include bronchitis (7%), bronchospasm and increased cough (3%), respiratory tract infection (15%), pharyngitis (3%), pneumonia (2%), rhinitis (2%) and sinusitis (2%).[1]

In our case, the patient was a known case of rheumatoid arthritis (RA) with pulmonary tuberculosis on LFM therapy for the last 10 years and presented to us with dry cough since 2 years, which was relieved after stopping the offending agent.

CASE PRESENTATION

A 40-year-old patient, a non-smoker, with no history of diabetes and hypertension, reported to our outpatient department with complaints of dry cough since 2 years, which increased since 2 months with minimal expectoration and loss of appetite. Her sputum for acid-fast bacillus (AFB) smear was positive, and her chest x-ray posterior–anterior (PA) view revealed a thick-walled cavity on the right middle zone (figure 1). So we started four-drug antitubercular treatment (ATT) consisting of rifampicin (R), isoniazid (H), ethambutol (E) and pyrazinamide (Z). On subsequent visits, she reported that there was no improvement in her symptom of cough, although there was improvement in other symptoms. However, the radiological examination revealed improvement. On re-evaluation, we found that she was a case of seropositive RA since the last 10 years and was on LFM monotherapy. As the long-term use of LFM has been associated with chronic cough, we advised her to stop LFM therapy. Cough markedly improved within a few days, and after 10 days, the patient was relieved completely. On re-introduction, the patient again started complaining of cough and hence was advised to discontinue LFM therapy. Now, the patient was referred to the rheumatology department for treatment of RA. After 2 months of ATT, her sputum for AFB became negative. E and Z were stopped. On chest x-ray right-sided cavity reduced in size (figure 2). After 8 months of ATT, the cavity almost disappeared (figure 3).

INVESTIGATIONS

X-ray chest PA view, sputum smear examination for AFB.

TREATMENT

Four-drug ATT: R, H, E and Z for 2 months followed by R and H for 4 months.

OUTCOME AND FOLLOW-UP

The patient was completely relieved of the cough on withdrawing from the offending drug and recovered completely from pulmonary tuberculosis on standard four-drug ATT gradually. She is now under our regular follow-up.

DISCUSSION

Cough is one of the most common respiratory symptoms. A wide variety of agents are known to cause it. ACE inhibitors can cause an isolated dry cough in the absence of bronchospasm and have been reported to

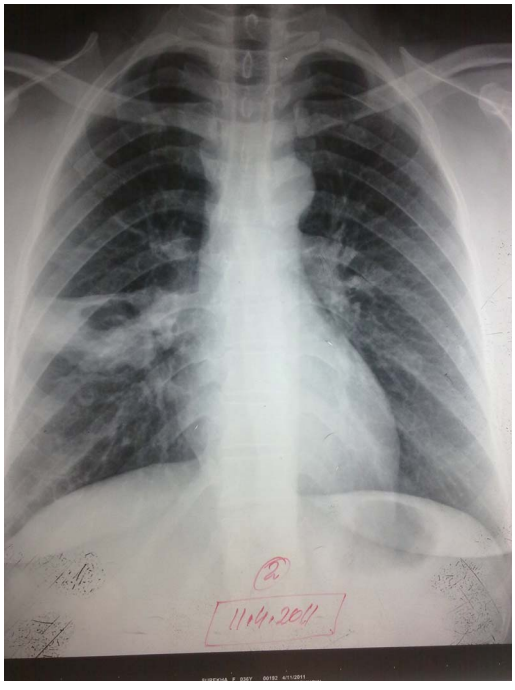

Figure 1 A large cavity in the right middle zone.

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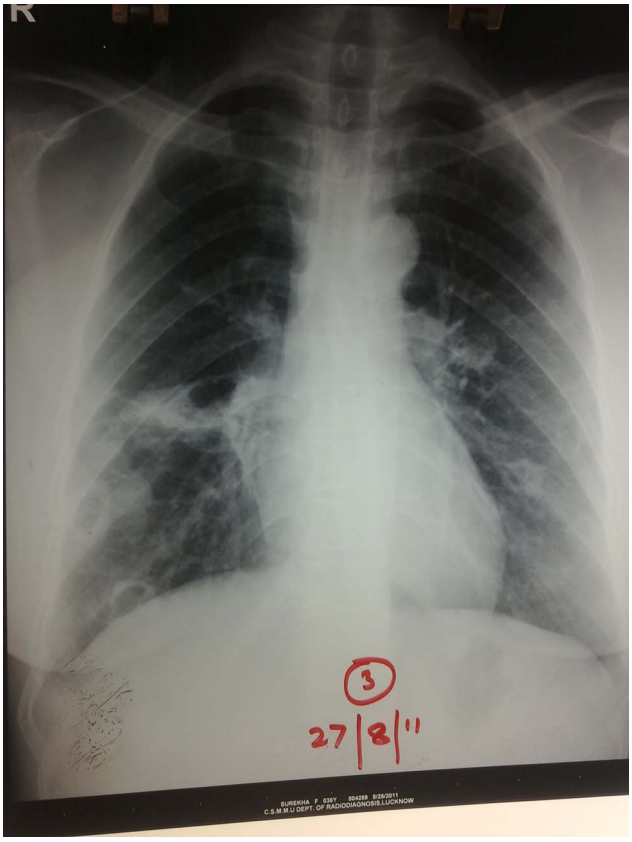

Figure 2 Reduction in the size of the cavity.

occur in 5–35% of patients using the medication.[2] The cough is thought to be due to elevated bradykinin levels caused by ACE inhibitor-induced inhibition of bradykinin metabolism.[3] Other drugs associated with cough and bronchospasm are: adenosine,[4] aspirin, β-blockers, contrast media, dipyridamole, interleukin-2 nitrofurantoin, penicillamine, pentamidine, sulfonamides and vinblastine (see table 1). The principal adverse effects of LFM therapy include diarrhoea, mild to moderate allergic reactions, reversible alopecia and transaminase elevations.[5] Patients of RA on LFM therapy have been reported to present with adverse events of recurrent pneumothorax,[6] granulomatous interstitial pneumonia,[7] and interstitial lung disease[8] and upper respiratory tract infection.[9] However, RA patients on LFM therapy have never reported having chronic dry cough. The clinicians should not forget the possibility of the phenomenon of idiosyncrasy. This particular case is an atypical case, which is the main reason for reporting this interesting case.

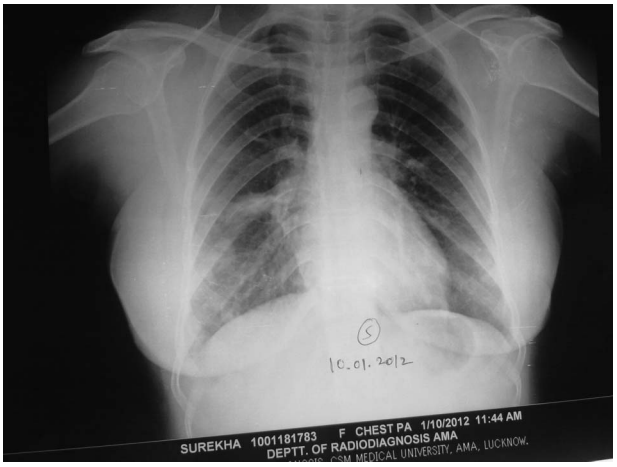

Figure 3 Disappearance of the tubercular cavity at the end of antitubercular treatment.

Table 1 Drugs causing cough as a side effect

Sl. No.	Name of drug
1	ACE inhibitors
2	Adenosine
3	Aspirin
4	β-Blockers
5	Contrast media
6	Dipyridamole
7	Interleukin-2
8	Nitrofurantoin
9	Penicillamine
10	Pentamidine
11	Sulfonamides
12	Vinblastine
13	Calcium channel blocker
14	Erythromycin
15	Amphotericin
16	Aminoglycosides
17	Inhaled steroids

Learning points

- Chronic cough can be drug induced.
- History is very important in making a diagnosis.
- Clinical features are unreliable indicators of treatment response in tuberculosis.
- Always consider replacing the offending drug with a safer one if possible.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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