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Leflunomide-induced interstitial pneumonitis: A rare occurrence in a case without underlying lung disease

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ABSTRACT

Pneumonitis from leflunomide is uncommon due to leflunomide's relatively favorable drug profile. Leflunomide-induced pneumonitis (LEIP) is a rare condition reported mainly in Asia. We present a case of LEIP from an accidental leflunomide overdose in the setting of concomitant methotrexate use and no underlying lung disease. Our patient was treated successfully with cholestyramine and steroids. Due to its high mortality, clinicians should be aware of this condition and its treatment.

1. Background

Leflunomide is a disease-modifying antirheumatic drug (DMARD) used for the treatment of rheumatoid arthritis. Due to its relatively favorable side effect profile, its use has been gaining popularity worldwide. Leflunomide can rarely cause pneumonitis in the presence of risk factors, as illustrated in this case.

2. Case presentation

A 78-year-old woman with a history of reported seronegative rheumatoid arthritis (RA) on chronic prednisone and methotrexate (MTX) presented with acute onset of shortness of breath.

On admission, she was afebrile and hemodynamically stable but hypoxic to 87%. Admission labs showed no leukocytosis (9770 cells/mcL), procalcitonin - 0.23 ng/mL (0.1–0.25 ng/mL - Low likelihood for bacterial etiology; Antibiotics discouraged) and normal cardiac biomarkers. She was lymphopenic at 480 cells/mcL (normal range: <600 cells/mcL), ESR and CRP were elevated at 98 (normal range: <25 mm/hr) and 24.6 (normal range: <0.5mg/dL), respectively. A respiratory exam revealed bilateral rhonchi and fine basilar crackles. She also had an erythematous rash on her chest and oral and nasal mucositis with epistaxis.

Before this admission, she was diagnosed with RA without any serology while she was a resident in another state, based on arthralgia and steroid responsiveness, and started on MTX and LEF by her primary care provider. Her serology with rheumatoid factor and anti-cyclic citrullinated peptide was rechecked and confirmed negative at our institution when she established care with Rheumatology here. She did not endorse joint swelling or morning stiffness, and her physical examination also did not reveal any evidence of active inflammatory changes. Subsequently, her prednisone dose was tapered from 30 mg daily to 10 mg due to negative serologies and no evidence of active disease while continuing her MTX as a steroid-sparing agent.

She had no history of lung disease, was a lifelong non-smoker without occupational exposures. She had no known allergies, inhalational exposures, or pets at home. Her arthralgia seemed to have been well controlled with prednisone and methotrexate.

Computed tomography (CT) showed diffuse bilateral consolidations and ground-glass opacities (GGO) with sub-pleural sparing (Fig. 1). An echocardiogram showed a left ventricular ejection fraction of 75% and no other abnormalities. Blood and sputum cultures, including legionella cultures, were negative. Methotrexate level checked on admission was normal at 0.13 mcmol/L (<20 mcmol/L). Her methotrexate was discontinued, and she was started on empiric antibiotics and diuretics as well as leucovorin. She later also became neutropenic and encephalopathic.

Due to lack of clinical improvement, a further review of her medication history revealed that she had taken leflunomide (LEF) 20mg three times daily, mistakenly taking a 3-month supply in one month and then continuing 20mg daily until one month before admission. Subsequently LEF metabolite teriflunomide level was checked and returned very high

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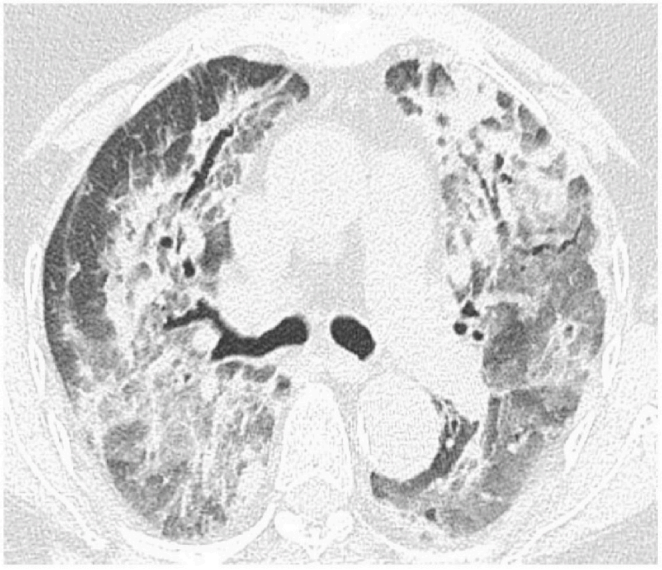

Fig. 1. Diffuse bilateral predominantly upper lobe peribronchovascular consolidative opacities associated with scattered regional ground-glass opacities, thickened interlobular septa, and diffuse bronchitic changes.

at 73,502 ng/mL (<20 ng/mL). She was consequently diagnosed with leflunomide-induced pneumonitis (LEIP). Treatment was initiated with cholestyramine at 8 g three times daily, and her steroid dose was also increased. Incidentally, her beta-*d*-glucan assay also came back elevated, and aspergillus galactomannan antigen was negative. The beta-*d*-glucan was thought to be a false positive result after previous albumin infusions and empiric cefepime she received before testing. She had already started clinically improving with cholestyramine and steroids even before starting trimethoprim/sulfamethoxazole. A bronchoscopy with bronchoalveolar lavage was deferred per patient and family request due to clinical improvement. Her shortness of breath significantly decreased, and she was weaned off oxygen. Her rash, and mucositis also improved, and neutropenia resolved. Nevertheless, she was started on trimethoprim/sulfamethoxazole on day 11 of her hospitalization, considering her severely immunocompromised status from steroids, methotrexate, and lingering toxic levels of LEF. Three weeks later, a repeat CT chest showed significant improvement with resolving GGO and improving coarse infiltrates in the lower lung (Fig. 2).

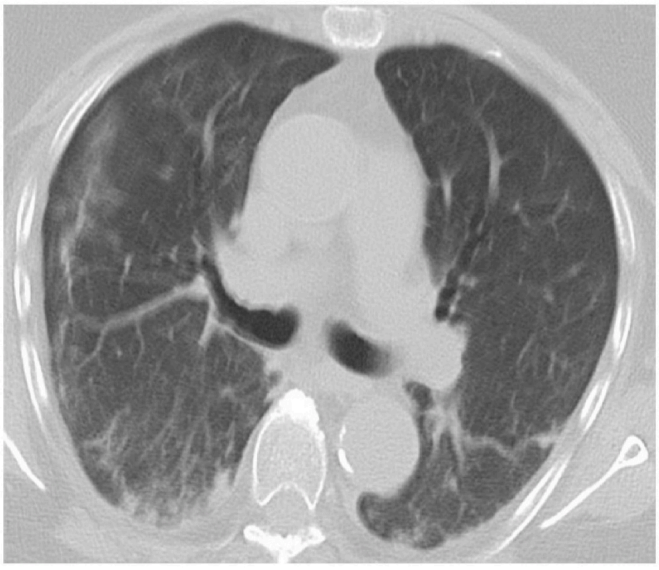

Fig. 2. Overall improved pulmonary appearance with resolving diffuse ground-glass opacities and improving coarse infiltrates in the lower lung zones.

3. Discussion

In rheumatoid arthritis (RA) patients with prior lung disease, leflunomide (LEF) has been considered a safer alternative to methotrexate due to its decreased risk of pneumonitis [1,2]. LEF is a nonbiological immunomodulatory prodrug that gets metabolized to its active metabolite teriflunomide. Teriflunomide suppresses the de novo synthesis of pyrimidine nucleotides [3,4].

With a worldwide prevalence of 0.02%, leflunomide-induced interstitial pneumonitis (LEIP) is a rare but severe condition with an associated mortality of around 20% [5]. LEIP is most frequent within the first 20 weeks of treatment [6]. LEF has a prolonged half-life of 15–18 days due to its significant entero-hepatic circulation. Therefore, LEIP may occur even after the cessation of the medication [7].

The risk for pneumonitis increases with underlying interstitial lung disease (ILD), history of methotrexate (MTX) use or methotrexate pneumonitis (MTX-P), the use of LEF loading doses, smoking, and low body mass index [8,9]. Most LEIP patients had prior MTX exposure as LEF is usually a second-line treatment after MTX failure or intolerance or used in combination with MTX in RA treatment [6,10]. Prior history of MTX-P confers a higher mortality risk in LEIP patients [6].

The fact that the incidence of LEIP is higher in Japan and Korea compared to the US and Europe seems to suggest that genetic polymorphisms may play a role in its pathogenesis [6]. Post-marketing LEF surveillance in Japan showed an incidence of LEIP at 1.2% in RA patients and, interestingly, 0.7% in those without prior ILD [7,8].

MTX-P has diagnostic criterion adopted from Kremer, Seales & McKendry, which incorporates clinical criteria like nonproductive cough, fever >38 °C, dyspnea of <8 weeks, tachypnea >28 breaths/min and additional tests which include oxygen saturation <90%, pulmonary infiltrates on chest imaging, leukocyte count <15000 mm3 and negative blood and bronchial aspirate cultures. LEIP, however, has no such predefined diagnostic criteria or differentiating criteria from MTX-P. Previous case studies have used the MTX-P diagnostic criterion [6,11].

LEIP usually presents with dyspnea on exertion and dry cough [3]. CT features can be variable and frequently include bilateral diffuse parenchymal ground-glass opacities or reticular opacities co-occurring with consolidative changes [12]. High-resolution CT chest (HRCT) with honeycombing changes can be seen in delayed presentations of LEIP. Lung biopsies from autopsy samples showed evidence of diffuse alveolar damage [6].

The proposed therapeutic range of teriflunomide is 50–100 μg/mL. Though non-pulmonary adverse reactions to LEF have not equated well with serum teriflunomide levels, its relationship to ILD is unknown. Plasma levels of teriflunomide may potentially help diagnose LEIP when LEIP is suspected after excluding alternate diagnoses [3,13].

Due to LEF's long half-life, LEIP usually does not promptly resolve with LEF withdrawal in sharp contrast to rapid amelioration of MTX-P with MTX withdrawal [3].

LEF pneumonitis is treated primarily by discontinuation of the LEF, steroid treatment, and accelerated drug elimination via cholestyramine administration [14]. LEF metabolite levels can persist in plasma for up to two years without drug elimination. Cholestyramine is a bile acid sequestrant that can rapidly promote LEF removal through inhibition of its enterohepatic recycling. The elimination half-life is thus reduced from around two weeks to around one day [15,16].

Our patient inadvertently loaded herself with LEF, and her onset of symptoms coincided with the initiation of a prednisone taper, which likely unmasked and accelerated her pneumonitis.

She showed clear signs of clinical recovery with rapid resolution of respiratory symptoms, improving skin rash, mucositis, and mental status, and increasing absolute neutrophil count with cholestyramine treatment.

Our case has constraints with lack of bronchoscopy and pathology data and confounding factors like MTX, possible RA, and possible pneumocystis jirovecii pneumonia.

There is a significant overlap between the symptoms for MTX-P and LEIP, and a normal level for MTX does not exclude MTX-P. However, our patient significantly improved following the addition of cholestyramine and methylprednisolone 30 mg daily (equivalent to prednisone 0.5 mg/kg/day for her compared to her admission dose of prednisone 10 mg daily). Given this improvement with a lower steroid dose and cholestyramine and supported by supratherapeutic levels of teriflunomide (>3500 x upper limit of normal), we felt it is reasonable to conclude that most of her symptoms are caused by LEF toxicity.

Regarding her possible diagnosis of rheumatoid arthritis, rheumatology at our institution was not convinced about this diagnosis due to the absence of RA symptoms, negative serology, and physical examination without any evidence of active inflammatory changes. The plan on discharge was to maintain her off MTX and LEF and continue to taper her steroid.

Regarding her positive beta-*d*-glucan, we think this was a false positive test secondary to receiving intravenous albumin and cefepime initially. The fact that our patient showed clinical improvement even before trimethoprim/sulfamethoxazole was given, with steroids and cholestyramine as opposed to expected worsening in the event she had pneumocystis jirovecii supports this. Nonetheless, she was still treated on day 11, considering her immunocompromised status from steroids, MTX, and LEF, and indication for trimethoprim/sulfamethoxazole prophylaxis.

While acknowledging our case's limitations as mentioned above, we aim to make clinicians aware of the potential of pneumonitis from LEF. LEIP is a diagnosis of exclusion and should exist in the differential for respiratory symptoms in this patient population to avoid delay in treatment with steroids and specifically cholestyramine washout therapy.

4. Conclusions

Our case report features a rare presentation of LEF pneumonitis in a patient without underlying pulmonary disease secondary to LEF toxicity in the setting of concomitant MTX exposure. Clinicians should have heightened awareness of LEF as a potential cause of diffuse parenchymal lung disease in this patient population as it can often masquerade as infectious pneumonia, exacerbation of autoimmune-ILD, or even another drug-induced pneumonitis. There are no definitive diagnostic criteria for LEIP; however, the finding of elevated teriflunomide levels can be suggestive after ruling out infection and other etiologies. Management involves cessation of LEF and a trial of cholestyramine with steroids. Early diagnosis is pertinent as treatment is proven to reverse the disease process effectively.

Prior presentations

American Thoracic Society Conference 2020.

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Declaration of competing interest

All the authors have seen and approved the manuscript. The authors report no conflicts of interest.

References

[1] R. Conway, C. Low, R.J. Coughlan, M.J. O'Donnell, J.J. Carey, Leflunomide use and risk of lung disease in rheumatoid arthritis: a systematic literature review and metaanalysis of randomized controlled trials, J. Rheumatol. 43 (5) (2016) 855–860.
[2] V. Saravanan, C. Kelly, Drug-related pulmonary problems in patients with rheumatoid arthritis, Rheumatology 45 (7) (2006) 787–789.
[3] Y. Hirabayashi, H. Shimizu, N. Kobayashi, K. Kudo, Leflunomide-induced pneumonitis in a patient with rheumatoid arthritis, Intern. Med. 45 (10) (2006) 689–691.
[4] I.S. Padda, A. Goyal, Leflunomide, in: *StatPearls.* Treasure Island (FL), 2021.
[5] R. Raj, K. Nugent, Leflunomide-induced interstitial lung disease (a systematic review), Sarcoidosis Vasc. Diffuse Lung Dis. 30 (3) (2013) 167–176.
[6] B. Chikura, S. Lane, J.K. Dawson, Clinical expression of leflunomide-induced pneumonitis, Rheumatology 48 (9) (2009) 1065–1068.
[7] T. Sawada, S. Inokuma, T. Sato, et al., Leflunomide-induced interstitial lung disease: prevalence and risk factors in Japanese patients with rheumatoid arthritis, Rheumatology 48 (9) (2009) 1069–1072.
[8] C. Kelly, Leflunomide and the lung, Rheumatology 48 (9) (2009) 1017–1018.
[9] S. Suissa, M. Hudson, P. Ernst, Leflunomide use and the risk of interstitial lung disease in rheumatoid arthritis, Arthritis Rheum. 54 (5) (2006) 1435–1439.
[10] G. Weigt Ae, M. Aringer, Leflunomide as a second line dmard after methotrexate has limited impact on rheumatoid arthritis in real life, BMJ Journals: Ann. Rheum. Dis. 76 (2017) 1200.
[11] G. Carretero, L. Puig, L. Dehesa, et al., Guidelines on the use of methotrexate in psoriasis, Actas Dermosifiliogr 101 (7) (2010) 600–613.
[12] F. Sakai, S. Noma, Y. Kurihara, et al., Leflunomide-related lung injury in patients with rheumatoid arthritis: imaging features, Mod. Rheumatol. 15 (3) (2005) 173–179.
[13] C.C. Laboratories, Technical Update • June 2016, 2016.
[14] J.H. Ju, S.I. Kim, J.H. Lee, et al., Risk of interstitial lung disease associated with leflunomide treatment in Korean patients with rheumatoid arthritis, Arthritis Rheum. 56 (6) (2007) 2094–2096.
[15] Llc USFaDA-S-Aus, *Leflunomide.* Revised August 31 (2010).
[16] J.G. Stine, J.H. Lewis, Current and future directions in the treatment and prevention of drug-induced liver injury: a systematic review, Expet Rev. Gastroenterol. Hepatol. 10 (4) (2016) 517–536.