CASE REPORTS

Strong Suspicion of Lung Toxicity Due to Riluzole

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Riluzole is a drug used in the treatment of amyotrophic lateral sclerosis. To date, reports of lung toxicity have been exceptional. We present the case of a 74-year-old man diagnosed with amyotrophic lateral sclerosis. Following 3.5 months of treatment with riluzole (Rilutek®), the patient began to present a clinical picture consisting of nonproductive cough, progressive dyspnea (even with slight exertion), weakness, and radiologic progression with the appearance of predominantly peripheral bilateral pulmonary infiltrates that did not respond to treatment with amoxicillin-clavulanic acid. Bacterial tests did not reveal the presence of germs, nor did other examinations suggest an alternative diagnosis. The patient did not resume treatment with the drug or undergo complementary procedures aimed at obtaining histologic samples. Nevertheless, the coincidence in time, lack of response to antibiotic treatment, remission of symptoms following withdrawal of the drug without initiating any other treatment except 40 mg/d of methylprednisolone for 6 days, absence of alternative diagnoses, and suggestive clinical and radiologic findings all together point to toxicity due to riluzole.

Key words: *Riluzole. Lung toxicity. Amyotrophic lateral sclerosis. Pulmonary infiltrates.*

Alta sospecha de toxicidad pulmonar por riluzol

El riluzol es un fármaco utilizado en el tratamiento de la esclerosis lateral amiotrófica. Hasta la fecha, las referencias de toxicidad pulmonar han sido excepcionales. Presentamos el caso de un varón de 74 años, diagnosticado de esclerosis lateral amiotrófica, que tras 3 meses y medio de tratamiento con riluzol (Rilutek®) inició un cuadro clínico consistente en tos no productiva, disnea progresiva hasta hacerse de pequeños esfuerzos, astenia sin fiebre y con progresión radiológica con aparición de infiltrados pulmonares bilaterales de predominio periférico que no respondieron al tratamiento con amoxicilina-ácido clavulánico. Los estudios bacteriológicos realizados no demostraron gérmenes y otras exploraciones tampoco apuntaron un diagnóstico alternativo. El paciente no accedió a la realización de pruebas complementarias destinadas a la obtención de muestras histológicas ni a la reintroducción del fármaco. No obstante, la coincidencia en el tiempo, la falta de respuesta al tratamiento antibiótico, la resolución del cuadro tras la retirada del fármaco sin instaurar otro tratamiento salvo 40 mg/día de metilprednisolona durante 6 días, la ausencia de diagnósticos alternativos y hallazgos clínicos y radiológicos indicativos apuntan a la toxicidad por el riluzol.

Palabras clave: *Riluzol. Toxicidad pulmonar. Esclerosis lateral amiotrófica (ELA). Infiltrados pulmonares.*

Introduction

Amyotrophic lateral sclerosis (ALS) is a degenerative motor neuron disease that affects adults. The disease progresses inexorably and mean survival is 3 years from the time of diagnosis. Treatment is palliative as no treatment exists that targets the cause of the disease. In 1996, the Food and Drug Administration of the United States of America approved the use of riluzole (Rilutek®), as the drug produced a modest clinical response and prolonged mean survival by approximately 2 months in 2 multicenter clinical trials.[1,2] Although some authors have voiced doubts regarding the cost-effectiveness of the treatment,[3,4] several countries have approved its use for treating ALS.

Riluzole is a benzothiazole and although its mechanism of action is not fully understood, it has been linked to reduced stimulation of the neurons by the amino acid glutamate.[5] Tolerance of the drug is usually good and increased respiratory symptoms that would indicate lung toxicity have not been observed in clinical trials either before or after the drug went on the market.[6,7] Cassiman et al,[8] however, recently linked the diagnosis of hypersensitivity pneumonitis to treatment with riluzole in a patient with ALS.

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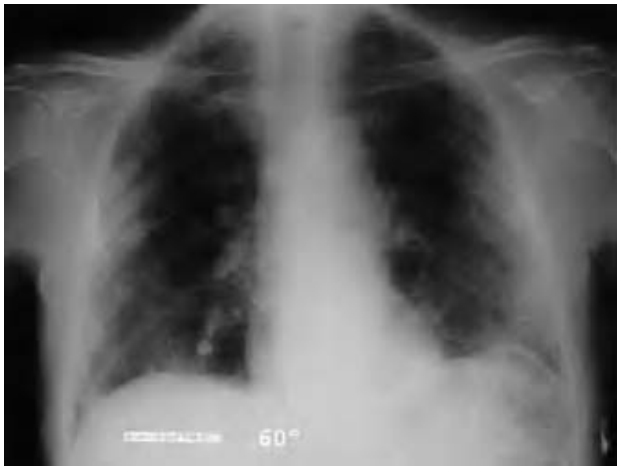

Figure 1. Predominately peripheral bilateral pulmonary infiltrates.

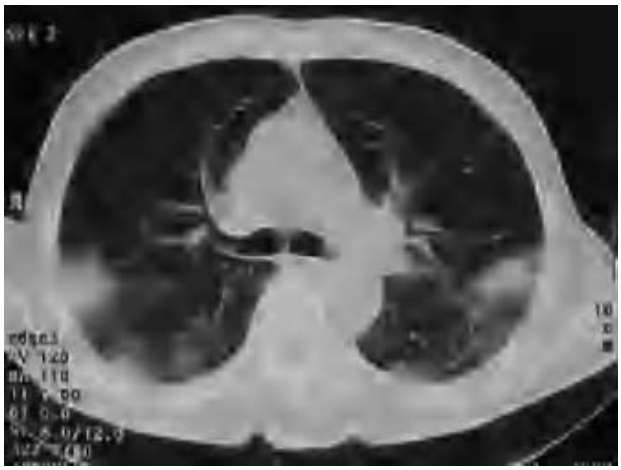

Figure 2. Predominately peripheral bilateral alveolar-interstitial infiltrates.

We present the case of a 74-year-old man diagnosed with ALS who, after being administered riluzole, developed a clinical picture consisting of nonproductive cough, dyspnea at rest, and bilateral pulmonary infiltrates revealed in a chest x-ray. The radiographic signs disappeared following withdrawal of the drug and administration of methylprednisolone for 6 days. We were unable to link the symptoms to any other cause.

Case Description

The patient was a 74-year-old man, ex-smoker of 37 pack-years, with no known allergies, diagnosed with ALS 10 months previously, and under treatment with riluzole, at a dosage of 50 mg/12 h, for the previous 5 months. He had developed a nonproductive cough 45 days before being admitted to our hospital. The patient was initially treated with amoxicillin—clavulanic acid at a dosage of 875 to 125 mg/8 h for 18 days until 5 days before admission but experienced progressive deterioration of symptoms consisting of increased nonproductive cough, dyspnea at rest, weakness, profuse sweating, tachypnea, but no fever at any time. On admission the patient was afebrile, blood pressure was 110/60 mm Hg, heart rate was 94 beats/min, and respiratory rate was 24 breaths/min. Shallow breathing was observed, but there were no other findings of interest. Blood gas analysis with oxygen administered through a mask at 2 L/min showed a pH of 7.46, PaO_2 of 67 mm Hg, $PaCO_2$ of 44 mm Hg, and bicarbonate (HCO_3^-) of 31 mEq/L. The hemogram showed 6200 leukocytes (68% neutrophils and 1% eosinophils) and an erythrocyte sedimentation rate of 74 mm in the first hour. There were high levels of fibrinogen (715 mg/dL), immunoglobulin (Ig) G (1960 mg/dL: IgG1, 1310 mg/dL; IgG4, 280 mg/dL), IgA (498 mg/dL), IgE (299 kU/L), and C-reactive protein (20 mg/L). Other results, including blood parameters, sugar, ions, kidney and liver function parameters, lactic dehydrogenase and its isoenzymes, angiotensin converting enzyme, IgM, antinuclear antibodies, anti-DNA antibodies, neutrophil anticytoplasmic antibodies, and serum tumor markers were within the normal ranges. The Mantoux test, blood tests for atypical germs and respiratory viruses, and urine tests for *Legionella pneumophila* serotype 1 and *Streptococcus pneumoniae* were negative. Despite the lack of fever, blood samples were taken on admission for culture, but no germs were isolated. The patient did not produce sputum; thus samples could not be obtained for bacteriological testing. The electrocardiogram and echocardiogram were normal. Skin tests for a battery of common lung allergens, including dust mites, pollens from weeds, trees, and grasses, fungi, and epithelia, were negative. X-ray and computed tomography of the chest revealed bilateral alveolar-interstitial infiltrates (Figures 1 and 2).

The fact that there was no fever, leukocytosis, or signs of respiratory infection led us to suspect that the lung involvement might be due to riluzole—the only drug the patient was taking. The drug was withdrawn and treatment was initiated with 40 mg/d of methylprednisolone for 6 days, after which treatment was stopped. After 72 hours, the patient showed a marked reduction in dyspnea, weakness, and infiltrates, and an increase in oxygen saturation. After 1 week, the infiltrates had disappeared and spirometry gave the following values: forced vital capacity (FVC), 1.34 (33%); forced expiratory volume in 1 second (FEV_1), 1.32 (47%); and FEV_1/FVC, 99%. Oxygen saturation at rest was 95% and there was no desaturation in the 6-minute walk test. The infiltrates did not reappear in follow-up examinations and the patient died of ALS 8 months later.

Discussion

Drugs are a frequent cause of iatrogenic effects and cause considerable morbidity and mortality. In a study carried out in the United Kingdom,[9] 6.5% of hospital admissions were linked to drug reactions and 2% of the patients affected (0.15% of all admissions to the hospital) died. The number of articles published on lung toxicity due to drugs has increased over the past 20 years.[10-12]

Riluzole has a neuroprotective effect in vitro and in vivo that reduces stimulation of neurons by glutamate. This effect has been linked to 3 possible mechanisms: inhibiting the release of glutamate and/or its receptors, blocking the voltage-dependent sodium channels, and reducing the entry of calcium into the neuron.[5] The usual

dosage is 100 mg/d in 2 doses and this is what was administered to our patient. Higher dosages increase toxicity without providing significant improvement.[2,13]

The drug is usually well tolerated and the most frequent side effects described are weakness and nausea in 15% to 20% of patients and an increase in liver enzymes (alanine aminotransferase) to more than 3 times baseline values in 10% to 15% of patients; patients should therefore be monitored while receiving this drug.[3,4]

In the case of drug-related lung toxicity, the suspected diagnosis may be based on the correlation between the time of appearance of symptoms and the time treatment is initiated, the disappearance of symptoms following withdrawal of the drug, and the low probability of other causes.[10,14] In the case of our patient, there was a correlation between the time riluzole was administered, the appearance of pulmonary infiltrates, the drop in PaO_2, and the disappearance of these symptoms following withdrawal of the drug. There were no other findings that indicated another disease and the patient was not taking any other drug that might have altered the metabolism of riluzole by the liver, although Sanderink et al[15] consider interaction with other drugs to be an improbable cause of toxicity.

Given the clinical status and the patient's principal illness, it was agreed with him that a course of treatment with corticosteroids would be initiated, although the dosages were lower than those established in other cases of drug toxicity.[8,15] For the same reason, it was decided at the outset not to perform biopsies using bronchoscopy or videoassisted thoracoscopy. The drug was not administered again and so the link between toxicity and the drug is strongly suspected but cannot be considered definitive. The clinical examination, radiology results, the increase in Ig concentrations and the response to withdrawal of the drug indicate a hypersensitivity reaction. Specific searches on MEDLINE, EMBASE, and the World Wide Web for drug-related lung toxicity (Pneumotox[12]) only returned the description by Cassiman et al[8] of a patient with clinical and radiologic findings and evolution similar to those described above and histologic findings of hypersensitivity pneumonitis.

Hypersensitivity reactions are idiosyncratic (type-B) reactions. Unlike the more frequent drug (type-A) reactions (80%-90%), where the effect depends on the dose, type-B reactions tend to be rare or exceptional events (10%-20%) that cannot be predicted despite knowledge of the drug's pharmacology.[16] Several studies have been published in which riluzole has been used as an antidepressant in specific cases of dyskinesia; it is therefore possible that the number of patients being treated with this drug will increase in the future.

In conclusion, the appearance of pulmonary infiltrates in patients being treated with riluzole, with no clinical data or findings in complementary tests that indicate a different diagnosis, should lead us to suspect possible lung toxicity. Improvement of the clinical picture following withdrawal of the drug, with or without administering corticosteroids will guide diagnosis.

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