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## Acute fibrinous and organizing pneumonia☆

### *Neumonía organizada fibrinoide aguda*

Acute fibrinoid and organizing pneumonia (AFOP) is a rare but serious histological variety of acute lung injury (ALI) that sometimes responds to treatment.

We report the case of a patient diagnosed with AFOP as a result of acute respiratory failure (ARF). A 70-year-old male patient, admitted to hospital in April 2020 for a 3/4-day history of dyspnoea at rest. In the targeted history-taking he reported dyspnoea on minimal effort during the previous 6 months. The following stand out in his personal history: HBP, obesity, hypercholesterolemia, ex-smoker (ICAT 40 packs/year), leukocytoclastic vasculitis and prostate cancer in 2013.

Given the epidemiological context, the symptoms, and the chest X-ray (bilateral alveolar-interstitial infiltrate), SARS-CoV-2 infection was established as the first diagnostic hypothesis, although the nasopharyngeal swab PCR and the serology were negative.

Despite initiating treatment protocol for Covid-19 (systemic corticosteroids and antibiotic therapy), progression was poor, requiring admission to the ICU and mechanical ventilation (MV). The patient experienced severe distress which prolonged his stay in the ICU for 2 months.

SARS-CoV-2, atypical bacterial serology, HIV, IGRA, bronchial aspiration, bronchoalveolar lavage and echocardiography were negative. Simultaneously, a wide range of antibodies were requested, including rheumatoid factor, ANA, anti-DNA, ANCA, inflammatory myopathy and anti-glomerular basement membrane antibodies, which were also negative. Chest CT scan showed increased 'ground glass' density in most of the lung parenchyma and patchy alveolar consolidation areas.

The study was completed with a surgical biopsy, reported as acute lung parenchymal injury leading to immature fibrosis, without hyaline membranes, with fibrinous exudate and foci of organizing pneumonia suggestive of AFOP.

Given this diagnosis, methylprednisolone boluses (500 mg/24 h for 3 days) followed by 1 mg/kg/24 h were administered, with slow clinical improvement allowing withdrawal of MV.

The patient is transferred to the ward, where cyclophosphamide was added; later replaced by mycophenolate mofetil. In spite of all this, no improvement was seen in 2 CT scan controls and the patient remained with dyspnoea at rest and oxygen therapy, dying 6 months after admission to a hospital for the chronically ill.

This disease was described as a result of the analysis of 17 suggestive cases of ALI, submitted to lung biopsy, which showed organized intra-alveolar fibrin deposition, areas of organizing pneumonia and patchy distribution.[1] Hyaline membranes, eosinophils, abscesses and granulomas must necessarily be absent for the diagnosis, which distinguishes it from classical interstitial lung diseases.

The usual symptoms are dyspnoea, fever and cough.[1,2] Radiologically, there is a diffuse infiltrate and ground-glass image[3] and the diagnosis of certainty requires lung biopsy.[2,3]

There are idiopathic cases and cases secondary to infectious diseases, autoimmune diseases, neoplasms, transplants and toxins.[2] Acute forms are usually fulminant, while subacute forms have a better prognosis when treatment is established.[1] The need for MV was identified as the only adverse prognostic factor, but when there is an underlying disease, it is often responsible for the increased mortality.[2]

Our case would correspond to a subacute, idiopathic form, which nevertheless had a fatal outcome that could be attributed to an established lung injury.

AFOP is probably underdiagnosed given its similarity to other lung conditions. Its form of presentation means that it can be interpreted as a pneumonia refractory to antibiotic treatment[4] and its radiological pattern is comparable to that of any interstitial lung disease.

The need for lung biopsy may cause a delay in diagnosis but it is of vital importance in cases such as this, as it may allow the patient to benefit from early treatment with steroids. There are no established recommendations regarding dose and treatment duration, finding variations from low doses to boluses of 250-1000 mg for 3 days.[3,5] The regimen is usually prolonged for months or years to avoid recurrences, both in idiopathic cases[4] as well as in those secondary to autoimmune diseases.[3]

Immunosuppressants such as mycophenolate mofetil, azathioprine and cyclophosphamide can be used in both acute and maintenance phases.[3,5]

In conclusion, this is a disease with high mortality, which should be considered in the context of ARF with unfavourable progression after ruling out the usual causes, in order to establish an effective treatment as soon as possible.

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## Conflict of interests

The authors declare that they have no conflict of interest.

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## Disulfiram hepatotoxicity: Report of three cases

### *Hepatotoxicidad por disulfiram: a propósito de tres casos*

*Dear Editor,*

Disulfiram is an alcohol deterrent that can cause liver damage. However, it can be difficult to reach a definitive diagnosis, leading to underestimate its potential hepatotoxicity.

### Case reports

*Case 1*

A 48-year-old woman presented in February 2020 with jaundice and malaise. She had been taking disulfiram for the last two months for alcohol addiction. Laboratory tests showed serum aspartate aminotransferase (AST) 2020 IU/L, alanine aminotransferase (ALT) 3467 IU/L, alkaline phosphatase (ALP) 254 IU/L, γ-glutamyltransferase (GGT) 80 IU/L and total bilirubin (TB) of 16.4 mg/dl. International normalized ratio (INR) was 1.36. Other potential causes of acute hepatitis were ruled out. Liver biopsy showed acute necrotic lesion with numerous eosinophils consistent with acute toxic hepatitis. Causality of disulfiram was probable according to the CIOMS/RUCAM scale (7 points).[1] The patient was discharged with no medication and she has evolved satisfactory with liver function tests within normal range in April 2020.

*Case 2*

A 44-year-old woman was referred to our Unit in March 2020, complaining of fatigue and nausea. She was on treatment with disulfiram for alcohol dependence since August 2019. Blood tests revealed AST 1709 IU/L, ALT 1406 IU/L, ALP 120 IU/L, GGT 111 IU/L, TB 15.1 mg/dl and INR of 1.49. Notably, an analytical test performed in October 2019 showed similar values in liver tests (AST 1395 IU/L, ALT 1134 IU/L, ALP 154 IU/L, GGT 191 IU/L, TB 9.1 mg/dl). Nevertheless, she continued with the same treatment. A complete etiological panel was negative and liver biopsy showed necrosis areas with inflammatory infiltration, compatible with acute hepatitis. When CIOMS/RUCAM scale was applied to assess disulfiram role, a score of 7 was obtained (probable). Following disulfiram discontinuation, liver enzymes returned to normal values 6 weeks later.

*Case 3*

A 53-year-old man, who was dentist and with no prior known liver disease, had self-medicated with disulfiram to give up alcohol consumption for ten days before symptom onset. He was admitted to the emergency department of his local hospital in June 2019 with diarrhoea and jaundice. At that time, laboratory tests showed AST 3431 IU/L, ALT 2133 IU/L, TB 23 mg/dl and an INR of 3.48. Disulfiram was stopped promptly and he was transferred to our liver Unit. Etiological studies were negative, except antinuclear antibodies positive 1/160 with nucleolar pattern. Abdominal ultrasound revealed a heterogeneous micronodular liver parenchyma with signs of portal venous hypertension. The calculated CIOMS/RUCAM score for disulfiram causality was 4 (possible). Four days after admission, the patient presented clinical worsening with hepatic encephalopathy, so liver transplant was performed, with satisfactory evolution. The explant showed important liver necrosis and signs of cirrhosis, without findings of steatohepatitis.

### Discussion

Disulfiram has been frequently used as an adjuvant in the treatment of alcohol use disorder (AUD), working as an alcohol deterrent. It is known that chronic therapy with disulfiram is associated with subclinical changes in liver function tests, with a predominantly hepatocellular damage pattern, but marked elevations of transaminases are uncommon.[2,3] It is recommended to perform liver function tests before starting disulfiram treatment and periodically during it, being contraindicated in presence of advanced liver disease. Anyhow, if hepatitis is noticed, it is indicated to stop disulfiram as soon as possible.

It could be interesting to debate some issues: firstly, patients with harmful alcohol intake may have already pre-existing liver disease, which can increase the risk of developing hepatotoxicity, so disulfiram prescription should be done with extremely caution. Secondly, alcoholic hepatitis can cause a clinical picture similar to DILI, so liver biopsy can be useful in differential diagnosis. Lastly, although ACLF due to non-alcohol-related cause, such as disulfiram-induced liver injury, is an indication of liver transplant, short term alcohol abstinence and consequently the possibility of relapse in alcohol consumption after transplantation could raise ethical dilemmas.[4]

We would like to highlight that these three cases described above have been seen in a short period of time, probably related to an increased use of disulfiram in the last months due to the withdrawal from the market in Spain in July 2019 of calcium carbimide, which contrasts with the very small number of cases recorded in the large DILI registries.[5] In view of the above, we can hypothesize that this trend will change in the future.

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