Pulmonary embolism in a patient with familial thrombophilia due to homozygotic genetic mutation in 2009C>T

Tromboembolia pulmonar en un paciente con trombofilia familiar de origen genético debida a homocigosis en mutación 2009C>T

Dear Editor,

Homozgyosis in 2009C>T mutation is a rare genetic alteration, previously undescribed in our country, which leads to coagulation disorders and a high tendency to suffer from thromboembolism. We present the case of an 84-year old male patient with a history of HBP, atrial fibrillation, chronic cardiac failure, implanted pacemaker and a biological mitral prosthesis, who was also recently diagnosed with inherited thrombophilia (homozgyosis in 2009C>T mutation). He was under treatment with 4 mg acenocoumarol (prior INR of 1.4 a week before admission, and 2.2 20 days before), 80 mg/24 h valsartan, 40 mg/24 h furosemide, 25 mg/48 h spironolactone, 20 mg/24 h pantoprazole, 160 mg/12 h megestrol, 52.5 µg/h one patch and a half/72 h buprenorphine TTS, 650 mg/8 h paracetamol, 50 mg/8 h diclofenac, 16 mg/12 h betaistine, 50 mg/12 h sulphride, 5 mg/24 h finasteride, 1 mg/24 h lorazepam, 10 mg/24 h citalopram, 0.5 mg/24 h risperidone and 25 mg/24 h quetiapine.

The patient was hospitalised due to presenting sudden-onset dyspnoea at rest. Previously, he had been independent for basic every day activities and walking, but over the course of the preceding month he presented pronounced functional decline, to the point of being bedridden. Initial diagnostic tests showed a pacemaker rhythm of 72 bpm on ECG and mild normocytic anaemia as well as leukocytosis with neutrophilia, mild thrombocytopenia (haematocrit: 36.8%, Hb: 12.2 g/dl, mean corpuscular volume: 97.7 fl, leukocytes: 14.5 × 10^9/L, with 83.4% of neutrophils and platelets 92 × 10^9/L), and significant renal failure (creatinine: 7.1 mg/dl), with marked uraemia (urea: 420 mg/dl) and moderate-serious hyperkalaemia (K 7.1 Eq/mL). The remaining ions were normal (Na 139 Eq/mL, ionc Ca 4.5 mg/dl). Cardiac enzymes were determined, and the result was creatine kinase 63 U/I and troponin T-HS of 202.6 ng/dl. The coagulation study revealed a prothrombin activity of 4%, Quick’s time 199.2 s, activated partial thromboplastin time 1.53 s and INR 20.12, with an initial D dimmer of 119,468 ng/ml (laboratory cut-off: 500). Arterial blood gas analysis detected: pH 7.384, pCO2 13.6 mmHg, pO2 89 mmHg, HCO3 13.3 mmol/L and 94.5% O2 saturation. Brain natriuretic propeptide was 4702 pg/ml. Thoracic X-ray showed no acute evolution findings. Abdominal ultrasound scan showed decreased kidney size for both kidneys and pronounced parenchymal atrophy. Due to the previous findings, treatment was initiated with intravenous sodium heparin, furosemide perfusion and fluid therapy. Upon suspicion of pulmonary thromboembolism, echocardiogram was requested with the following results: mildly dilated left ventricle with moderate-septal hypertrophy, preserved systolic function, moderately enlarged left atrium, pronounced aortic valve sclerosis with mild stenosis and moderate aortic insufficiency, mild enlargement of the right cavities with conserved right ventricular function, mild tricuspid insufficiency and presence of moderate pulmonary hypertension, with a pulmonary blood pressure of 48 mmHg. Later, a Doppler ultrasound scan of the lower limbs was completed, which showed the left internal saphenous vein with intraluminal echogenic content, which included peripheral linear calcification, compatible with superficial venous thrombosis. In light of these findings, even in renal failure, we decided to order a pulmonary scintigraphy, which detected subsegmental perfusion defects in the apical-posterior segment of the left upper lobe and in the apical segment of the right upper lobe. After withdrawal of sodium heparin and establishment of new oral anticoagulation, the platelet count normalised. Gait rehabilitation was initiated with good initial tolerance to standing position, proceeding to recovery of ambulation. The polypharmacy was reduced, with suspension of buprenorphine, betaistine, sulphride, diclofenac, citalopram, megestrol, quetiapine and risperidone.

References

Jose M. Trejo-Gabriel-Galán a,b, Naroa Arenaza-Basterrechea a, Maria J. Sedano-Tous a

a Sección de Neurología, Hospital Universitario de Burgos, Burgos, Spain
b Servicio de Neurología, Hospital Universitario Marqués de Valdecilla, Santander, Cantabria, Spain

* Corresponding author.
E-mail address: jtrejoggy@gmail.com (J.M. Trejo-Gabriel-Galán).

Drug-induced liver injury caused by simvastatin associated with antinuclear antibodies

Hepatotoxicidad por simvastatina con elevación de anticuerpos antinucleares

Dear Editor,

There have been reports of autoantibodies detected in some cases of drug-induced hepatotoxicity, although only a few medications are strongly associated with this phenomenon.

We present the case of a 66-year-old female patient who presented hepatotoxicity caused by simvastatin, with an elevated number of antinuclear antibodies (ANA). The patient had high blood pressure managed with diet, and she did not consume alcohol or herbal products. In the follow-up blood test after taking simvastatin 20 mg/day for 5 months, glutamate-pyruvate transaminase (GTP) was 92 IU/l and glutamate-oxaloacetic transaminase (GOT) 55 IU/l, while normal levels of gamma-glutamyl transpeptidase, bilirubin and alkaline phosphatase were detected. The patient was asymptomatic, and her physical examination was normal. Two months later, GTP was 102 IU/l, GOT 57 IU/l and ANA titre 1/320, with a homogeneous pattern. Anti-smooth muscle antibodies, anti-mitochondrial antibodies, immunoglobulins and proteinogram, as well as her liver ultrasound scan and the remaining hepatopathy study, were all normal. It was decided that simvastatin should be suspended, and, one month later, ANA levels became negative and transaminase levels were normalised.

Classic autoimmune hepatitis symptoms may be initiated by drug-induced hepatotoxicity. In 90% of cases, this is attributed to minocycline and nitrofurantoin, although there is documentation attributing it to statins. It seems to be idiosyncratic in nature, with a mainly hepatocellular pattern. It develops almost exclusively in females but, unlike the classic type, it is self-limited and it does not recur once treatment with corticosteroids is discontinued, nor does it develop into cirrhosis. Its clinical spectrum is broad, ranging from being asymptomatic to causing fulminant liver failure.

As far as its aetiology is concerned, genetic factors are essential. There are polymorphisms that determine the means to metabolise the drug and the intensity of the inflammatory and immunological response. On the other hand, there are genes belonging to the major histocompatibility complex that may modulate the neoantigen presentation and lymphocyte activation.

The pathogenetic basis resides in the loss of immune tolerance, which starts when a drug-reactive metabolite is developed. Their covalent bond to a hepatocyte surface protein gives rise to a neoantigen. This neoantigen activates the immune system and, thus, the damage only persists for as long as the drug is administered.

In this case, according to the CIOMS Scale, the causal relationship between simvastatin and the aforementioned symptoms is probable (8 points), and once the drug was suspended, the problem resolved in a month, as described in the medical literature.

The distinction between autoimmune-like hepatitis and other forms of drug-induced liver damage is made based on the presence of autoantibodies.

Treatment consists of suspending the causative agent and administering corticosteroids if the damage is significant. To continue administering the drug would cause chronic and progressive liver damage. It is also recommended to watch for the development of autoimmune diseases in the long term, since it has been observed that there is a persistent subclinical immune response.

References