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SCIENTIFIC LETTER

Severe hypertriglyceridaemia and hypervitaminosis D secondary to multiple myeloma

Hipertrigliceridemia e hipervitaminosis D graves secundarias a mieloma múltiple

We describe in this article a case report of a 75-year-old woman who was admitted to the Short Stay Unit of our hospital in March 2023 due to a urinary infection associated with fever. She had a personal history of hypertension, osteoarthrosis, osteoporosis, irritative bowel syndrome and an IgG kappa multiple myeloma diagnosed in 2011 in advanced stage III-A. She had received five lines of active treatment for her myeloma and, as a lack of response was observed, the Haematology Department decided to withdraw active chemotherapy treatment in May 2022. Her daily medication consisted in: Valsartan 80 mg/24 h, Furosemide 40 mg/24 h, Mebeverine 135 mg/8 h, Diazepam 2 mg/24 h, Zolpidem 10 mg/24 h, Escitalopram 20 mg/24 h, one Fentanyl Parch 100 mcg/h every 3 days, Paracetamol 1000 mg/8 h, four Pregabalin 25 mg pills a day and Omeprazole 20 mg/24 h.

The basal status of the patient was that she was completely dependent on others to perform basic daily activities and had to eat shredded meals due to dysphagia.

A complete blood test was performed, which included a lipid profile, liver function markers, renal function, electrolytes, PTH, 25-OH-vitamin D, vitamin B12 and a haemogram. The total cholesterol level was 11.84 mmol/L (458 mg/dl), HDL cholesterol 0.46 mmol/L (18 mg/dl), VLDL cholesterol 7.52 mmol/L (291 mg/dl) and triglycerides 16.44 mmol/L (1455 mg/dl). LDL cholesterol could not be calculated due to hypertriglyceridaemia. Moreover, the 25-OH-vitamin D levels were above the upper limit of detection (>154 ng/ml), whilst serum calcium remained within normal values. The patient had never had such high levels of triglycerides, cholesterol or 25-OH-vitamin D. To rule out an error in the sample, a new one was taken, resulting in similar values: triglycerides 16.62 mmol/L (1471 mg/dl), 25-OH-vitamin D >384.37 nmol/L (>154 ng/ml) and the eGF rate was 113 ml/min/1.73 m^2.

The anamnesis was completed with information obtained from the patient's daughter. She denied any changes in the patient's diet, and no sources of high fat or simple sugars were identified. She had not made any changes to her usual medication, and it was confirmed that the patient had not taken any vitamin D supplements. She did not present any limb oedemas or cutaneous xanthomas. Her last weight was 65 kg, measured in July 2022, and her height was 1.58 m, resulting in a body mass index of 26 kg/m^2. The daughter confirmed that she had not gained weight in recent months. Therefore, a secondary aetiology of the hypertriglyceridaemia was suspected. Possible secondary causes of hypertriglyceridaemia that should be considered include obesity, metabolic syndrome, diabetes mellitus, increased alcohol consumption, excessive caloric intake, hypothyroidism, kidney disorders (nephrotic syndrome), paraproteinemia, systemic lupus erythematosus, anorexia nervosa, glycogenosis, sepsis, pregnancy and drugs.[1]

It was decided to amplify the blood test with an HbA1c and TSH, to rule out undetected diabetes mellitus or hypothyroidism. Both results were normal: 5.27% and 5/63 mIU/L, respectively. Furthermore, the patient appeared to have a low BMI, did not consume alcoholic beverages and was not known to have any rare diseases such as systemic lupus erythematosus, glycogenosis, or anorexia nervosa, and none of the patient's current medications produced hypertriglyceridaemia. Glomerular filtration rate was normal, and proteinuria was negative.

Consequently, the most likely secondary cause of the hypertriglyceridaemia in this patient was paraproteinaemia. She had not been receiving active treatment for her multiple myeloma since May 2022 and no new blood tests that included triglycerides levels had been carried out until the current episode (Fig. 1a). This variant of multiple myeloma in which dyslipidaemia occurs is known as hyperlipidaemic myeloma.[2]

Hyperlipidaemic myeloma is a rare variant of multiple myeloma characterised by high triglycerides, LDL cholesterol levels and low levels of HDL cholesterol.[2,3] Its clinical course, pathophysiology and the best therapy remain unknown. A pathophysiological mechanism has been proposed in which the paraprotein might bind to IDL and LDL lipoproteins, interfering with its receptor-mediated hepatic clearance. Moreover, it has also been suggested that paraprotein might bind to lipoprotein lipase reducing triglyceride metabolism.[2,3] The largest review of this pathology was made by Misselwitz et al. in 2010, in which they reviewed 53 patients between 1937 and 2007. The most common type of myeloma was IgA in 53.3% of cases, whereas in conventional multiple myeloma, the most common type is IgG in 51.5% of cases.[2] Recently, Rahman et al. detected the first case of hyperlipidaemic myeloma due to a light chain subtype.[3]

Misselwitz et al. observed that hyperlipidaemic myeloma can present either as an analytical alteration only or it can present with atherosclerosis, cutaneous xanthomas and/or hyperviscosity syndrome with either visceral or lower limb ischaemia or haemorrhages.[2] Our patient did not present any cutaneous xanthomas in the physical examination.

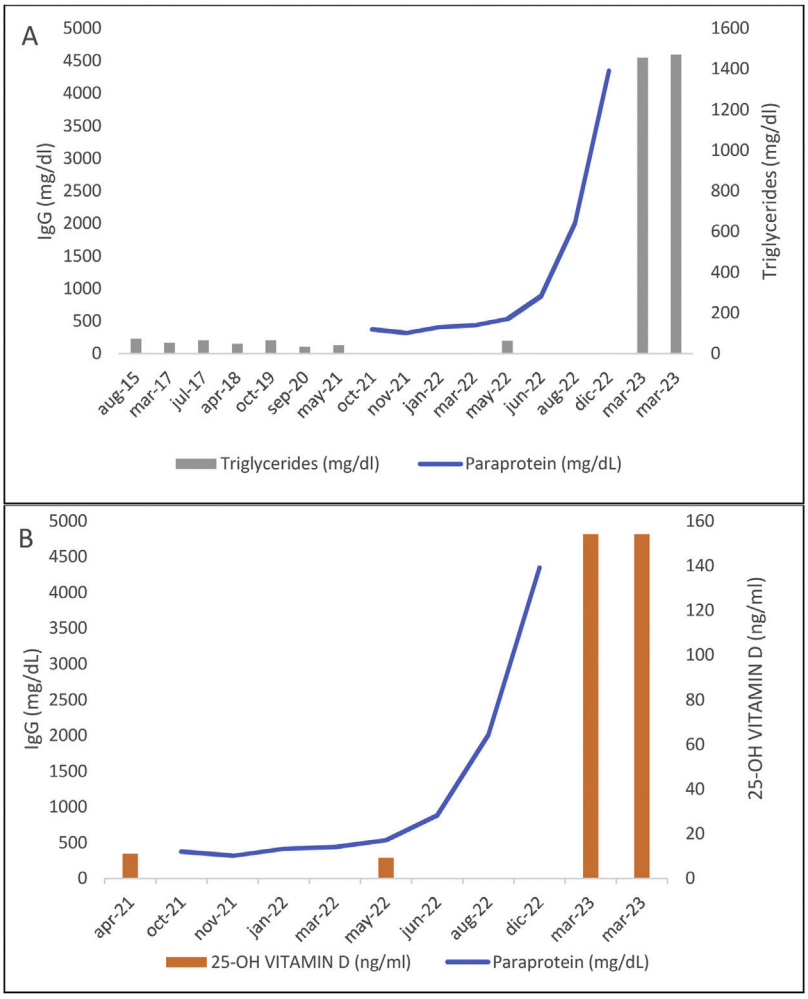

Figure 1 Relationship between paraprotein, triglycerides (A) and 25-OH-vitamin D levels (B). The sudden rise in triglycerides (A) and 25-OH-vitamin D (B) levels matches with the increase in paraprotein levels, even though they were not measured at the same time. May 2022 was the month when the active treatment against her myeloma was interrupted.

As for the hypervitaminosis D, the main cause is overconsumption of oral supplements.[4] However, the patient had not taken any vitamin D supplements. Ong et al. reported a case of hypervitaminosis D in a woman with IgG multiple myeloma who did not present any signs of toxicity.[5] They concluded that paraprotein could interfere with immunoassay techniques used to measure vitamin D, resulting in high artefactual levels. Liquid chromatography–mass spectrometry was later performed and confirmed normal values in the same patient.[5] This is the most likely cause of hypervitaminosis D in our patient, as she previously presented low levels (Fig. 1b). However, we were not able to perform a confirmatory technique as the patient died from myeloma progression soon after our initial evaluation.

Hypervitaminosis D did not require any treatment as it was considered an artefactual finding.

Regarding the hypertriglyceridaemia, the use of lipid-lowering drugs does not effectively reduce lipid levels as the hyperparaproteinaemia persists.[2,3,6] Lipid levels are reduced or even normalised when active treatment against multiple myeloma is applied and a good response is observed.[2,3,6] Misselwitz et al. reported a considerable improvement or normalisation in triglyceride levels in 14 out of 33 patients who received chemotherapy, whereas only 1 out of 19 patients receiving fibrates normalised triglyceride levels.[2] Therefore, lipid-lowering treatments were not initiated in this patient due to the probable poor response and the bad medical status of the patient.

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Diabetes and jaundice in young patients. The importance of extrapancreatic manifestations in the typing of diabetes mellitus

Diabetes e ictericia en paciente joven. La importancia de las manifestaciones extrapancreáticas en la tipificación de la diabetes mellitus

Diabetes mellitus (DM) is a highly prevalent disease with a wide aetiopathogenesis. Type 2 DM is, by far, the most common cause of diabetes in the world, accounting for 85–95% of cases diagnosed as diabetes.[1] Among other factors, genetic factors resulting from the interaction of several genes play a role in its aetiopathogenesis. However, monogenic diabetes is a clinically heterogeneous disorder characterised by diabetes diagnosed at an early age (<30 years) with autosomal dominant inheritance and negative autoimmunity. The genes involved control the development and function of pancreatic β-cells. Prevalence studies estimate that it represents 1%–5% of all cases of DM[2] with maturity-onset diabetes of the young (MODY) the most common form. Monogenic diabetes is a diagnostic challenge given its heterogeneity and confusion with other subtypes of DM, and it is globally underdiagnosed. Clinical suspicion is essential to indicate a genetic study, and the study of possible extrapancreatic manifestations is important. The genetic study allows us to make a precise diagnosis, initiate personalised treatment and provide genetic advice to family members. Furthermore, jaundice and asymptomatic hyperbilirubinaemia are common clinical problems which can be caused by a wide variety of disorders, including excessive bilirubin production, impaired bilirubin conjugation, biliary obstruction and hepatic inflammation.[3]

We present the case of a 34-year-old male being investigated by Gastroenterology for jaundice, with no relevant history except for a self-limiting episode of hypertransaminasaemia in 2013. He did not have any toxic habits and was not on any long-term treatments. Progressive jaundice of the skin, pruritus and weight loss were notable along with choluria and acholia, with no fever or abdominal pain. Weight 82 kg, height 182 cm, BMI 24.76 kg/m^2. Blood tests showed glucose 151 mg/dL, LDH 248 IU/L (140–180 IU/L), AST 111 IU/l (8–33 IU/L), ALT 309 IU/L (4–36 IU/L), GGT 375 IU/L (6–28 IU/L), alkaline phosphatase 269 IU/L (44–147 IU/L), total bilirubin 14.8 mg/dL (0.1–1.2 mg/dL), direct bilirubin 9.6 mg/dL (<0.3 mg/dL), ferritin, alpha-1-antitrypsin and plasma copper normal, with negative hepatic autoimmunity. Complete blood count and coagulation normal. Abdominal ultrasound including the urinary tract normal. Magnetic resonance cholangiopancreatography showed normal liver and atrophy of the body of pancreas. Liver biopsy with signs of cholestasis without inflammation or fibrosis. Laboratory tests during admission showed fasting hyperglycaemia (154 and 160 mg/dL) diagnostic of DM, with HbA1c 5.5%. Given this discordance, the study was extended to two months with increasing basal blood glucose (224 mg/dL) and HbA1c also increasing (7.1%), C peptide (CP) 2.24 ng/mL (0.81–3.85), autoimmunity with negative antiGAD Ab and anti-IA2 Ab 14.1 U/mL (normal <7.5 U/mL) and low faecal elastase (103, normal >200). Elevated bile acids in the blood (>200, normal <10).

Therapy with insulin glargine was started at a rate of 0.2 IU/kg/day (16 IU) for onset of diabetes and, after having ruled out the most common causes of cholestasis (bile duct obstruction, sclerosing cholangitis, primary biliary cirrhosis), a panel of 75 genes related to cholestasis and associated syndromes was requested. Results showed a partial deletion of the long arm of chromosome 17 (17q12) which was encompassing the HNF1B gene, the gene responsible for MODY-5 diabetes and which could explain the hepatobiliary condition. Treatment was initiated with ursodeoxycholic acid 500 mg every eight hours, pancreatin 25,000 IU, eight tablets daily, and ultra-rapid insulin for corrections. At the eight-month follow-up, treated with 12 IU of basal insulin without requiring ultra-rapid insulin corrections, the HbA1c was 5.9% and CP remained normal (1.79 ng/mL).

In our patient, the development of cholestasis coinciding with the diagnosis of diabetes is an uncommon manifestation, with very few cases described in the literature,[4] but which must be taken into consideration in order for correct typing. For this reason, we have included in the differential diagnosis genetic cholestasis associated with DM (Fig. 1), such as benign recurrent intrahepatic cholestasis type 1, although none of the genes involved were mutated in our patient. As in this case, the aetiopathogenesis of diabetes may not be evident at onset. The presence of positive anti-IA2 Abs points to an autoimmune origin, the genetic study to a monogenic aetiology and pancreatic atrophy with exocrine pancreatic insufficiency (EPI) and the recent onset