

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, osteoarthritis, 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 m².

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/m². 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

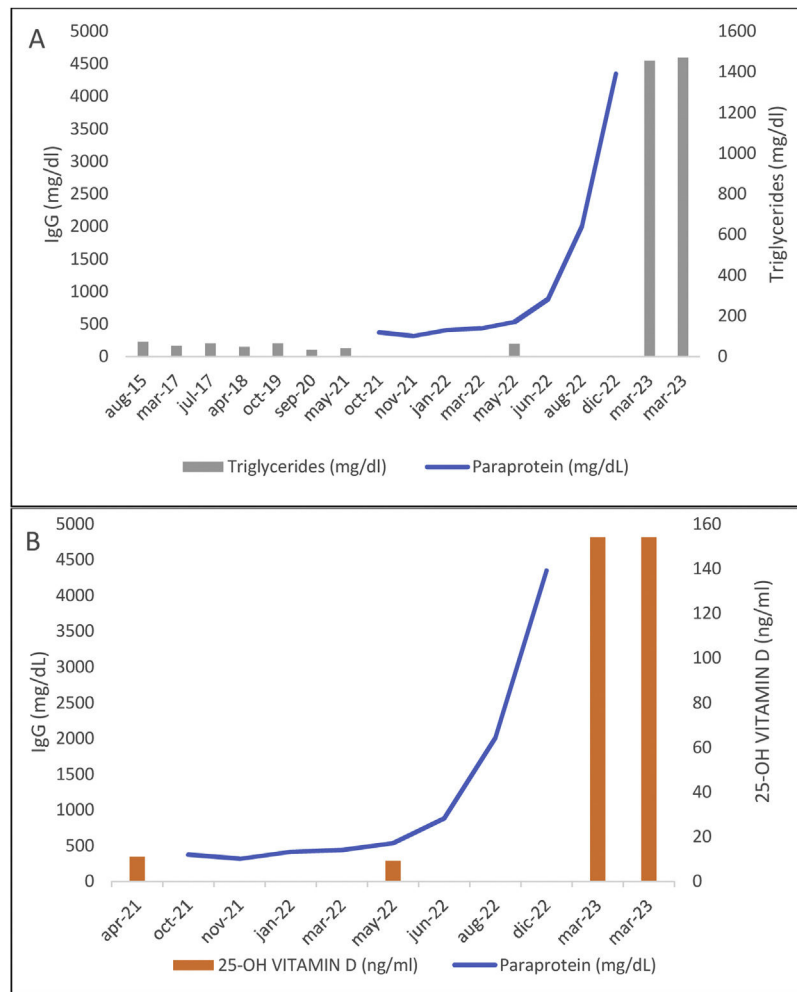


Figure 1 Relationship between paraprotein, triglycerides (A) and 25-OH-vitamin D levels (B). The sudden rise in triglycerides (A) and 25-OH-vitamin D (B) levels matches with the increase in paraprotein levels, even though they were not measured at the same time. May 2022 was the month when the active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

ischaemia or haemorrhages.² Our patient did not present any cutaneous xanthomas in the physical examination.

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



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

La diabetes mellitus (DM) es una enfermedad muy prevalente con una amplia etiopatogenia. La DM tipo 2 es, con diferencia, la causa más frecuente de diabetes en el mundo, y supone 85-95% de los casos diagnosticados como diabetes¹. En su etiopatogenia intervienen, entre otros, factores genéticos fruto de la interacción de varios genes. Sin embargo, la diabetes monogénica es un trastorno clínicamente heterogéneo caracterizado por diabetes diagnosticada en edad temprana (< 30 años) con herencia autosómica dominante y autoinmunidad negativa. Los genes implicados controlan el desarrollo y la función de las células β-pancreáticas. Los estudios de prevalencia la estiman entre 1 a 5% del total de casos de DM² y la diabetes de inicio en adultos jóvenes (MODY) la forma más frecuente. La diabetes monogénica supone un reto diagnóstico dada su heterogeneidad y confusión con otros subtipos de DM, y está globalmente infradiagnosticada. La sospecha clínica es fundamental para indicar el estudio genético, siendo importante el estudio de posibles manifestaciones extrapancreáticas. El estudio genético nos permite realizar el diagnóstico preciso, iniciar el tratamiento personalizado y proporcionar consejo genético a los familiares. Por otra parte, la ictericia y la hiperbilirrubinemia asintomática son problemas clínicos frecuentes que pueden ser causados por una amplia variedad de trastornos, que incluyen la producción excesiva de bilirrubina, la conjugación alterada de la bilirrubina, la obstrucción biliar y la inflamación hepática³.

Presentamos el caso de un varón de 34 años en estudio por el Servicio de Digestivo por ictericia, sin antecedentes de interés salvo por un episodio de hipertransaminasemia autolimitada en 2013. No presentaba hábitos tóxicos y no recibía tratamientos crónicos. Destacaba ictericia cutánea progresiva, prurito y pérdida ponderal junto a coluria y acolia, sin fiebre ni dolor abdominal. Peso 82 kg, talla

182 cm, IMC 24,76 kg/m². Analítica con glucosa 151 mg/dL, LDH 248 UI/L (140-180 UI/L), AST 111 UI/L (8-33 UI/L), ALT 309 UI/L (4-36 UI/L), GGT 375 UI/L (6-28 UI/L), fosfatasa alcalina 269 UI/L (44-147 UI/L), bilirrubina total 14,8 mg/dL (0,1-1,2 mg/dL), bilirrubina directa 9,6 mg/dL (< 0,3 mg/dL), ferritina, alfa-1-antitripsina y cupremia normales, con autoinmunidad hepática negativa. Hemograma y coagulación normales. Ecografía abdominal incluyendo la vía urinaria normal. Colangiografía con hígado normal y atrofia del cuerpo pancreático. Biopsia hepática con signos de colestasis sin inflamación ni fibrosis. Las analíticas durante el ingreso mostraban hiperglucemias en ayunas (154 y 160 mg/dL) diagnósticas de DM, con HbA1c 5,5%. Dada esta discordancia se amplió el estudio a los dos meses con glucemia basal en aumento (224 mg/dL) y HbA1c también en aumento (7,1%), péptido C (PC) 2,24 ng/mL (0,81-3,85), autoinmunidad con Ac antiGAD negativos y Ac antiIA2 14,1 U/mL (normal < 7,5 U/mL) y elastasa fecal baja (103, normal > 200). Ácidos biliares en sangre elevados (> 200, normal < 10).

Se inicia terapia con insulina glargina a razón de 0,2 UI/kg/día (16UI) ante el debut diabético y, tras haber descartado las entidades etiológicas más frecuentes de colestasis (obstrucción de vías biliares, colangitis esclerosante, cirrosis biliar primaria), se solicitó un panel de 75 genes relacionados con colestasis y síndromes asociados, dando como resultado una delección parcial del brazo largo del cromosoma 17 (17q12) que abarca el gen HNF1B, gen responsable de diabetes MODY-5 y que podría explicar el cuadro hepatobiliar. Se instauró tratamiento con ácido ursodesoxicólico 500 mg cada ocho horas, pancreatina 25.000 UI, ocho comprimidos diarios, e insulina ultrarrápida para correcciones. En la revisión a los ocho meses, en tratamiento con 12 UI de insulina basal sin requerir correcciones de insulina ultrarrápida, presentaba HbA1c 5,9% y el PC se mantuvo conservado (1,79 ng/mL).

En nuestro paciente, la aparición de colestasis coincidiendo con el diagnóstico de diabetes constituye una manifestación infrecuente con muy pocos casos descritos en la literatura⁴, pero a tener en cuenta para su correcta tipificación. Por ello, hemos incluido en el diagnóstico diferencial las colestasis genéticas que se asocian a DM (fig. 1), como la colestasis intrahepática benigna recurrente tipo 1, aunque ninguno de los genes implicados estaba mutado en nuestro paciente. Como sucede en este caso, la etiopatogenia de la diabetes puede no ser evidente al debut. La