At present, BRAF inhibitors are first-line drugs. For BRAF V600 mutation-negative patients, it is advisable to look for other MAPK pathway abnormalities, which can be treated with a MEK inhibitor.

In conclusion, the first sign of central nervous system involvement due to ECD in our patient was diabetes insipidus.[12] The manifestation of prior skeletal signs as well as characteristic radiological and histological findings led to the patient's definitive diagnosis; hence, a comprehensive medical history by endocrinology was of particular importance in suspecting this rare disease.

References

1. Starkebaum G, Hendrie P. Erdheim-Chester disease. Review. Best Pract Res Clin Rheumatol. 2020;34:101510.
2. Papo M, Emile JF, Maciel TT, Bay P, Baber A, Hermine O, et al. Erdheim-Chester disease: a concise review. Review. Curr Rheumatol Rep. 2019;21:66.
3. Chertok Shacham E, Ishay A. Central diabetes insipidus as an early presentation of Erdheim-Chester disease. Case reports. Isr Med Assoc J. 2018;20:586–7.
4. Haroche J, Arnaud L, Cohen-Aubart F, Hervier B, Charlotte F, Emile JF, et al. Erdheim–Chester disease. Curr Rheumatol Rep. 2014;16:412.
5. Toro Galván S, Planas Vilaseca A, Michalopoulou Alevras T, Torres Díaz A, Suárez Balaguer J, Villabona Artero C. Alteraciones endocrinas en las histiocitosis de la región hipotálamo hipofisaria. Endocrinol Nutr. 2015;62:72–9.
6. Amor BB, Sayadi H, Jemel M, Mrabet H, Hadhri R, Slim T, et al. Erdheim-chester disease revealed by diabetes insipidus. Case reports. Pan Afr Med J. 2019;33:293.
7. Alaya W, Zantour B, Ben Salem W, Chebbi W, Sfar HM. Difficult diagnosis of Erdheim Chester disease revealed by central diabetes insipidus. Rev Med Liege. 2017;72:436–8.
8. Khamseh ME, Mollanai S, Hashemi F, Rezaizadeh A, Azizi F. Erdheim-Chester syndrome, presenting as hypogonadotropic hypogonadism and diabetes insipidus. J Endocrinol Invest. 2002;25:727–9.
9. Courtillot C, Laugier Robiolle S, Cohen Aubart F, Leban M, Renard-Penna R, Drier A, et al. Endocrine manifestations in a monocentric cohort of 64 patients with Erdheim-Chester disease. Observational study. J Clin Endocrinol Metab. 2016;101:305–13.
10. Diamond EL, Dagna L, Hyman DM, Cavalli G, Janku F, Estrada-Veras J, et al. Consensus guidelines for the diagnosis and clinical management of Erdheim-Chester disease. Practice guideline. Blood. 2014;124:483–92.
11. Goyal G, Heaney ML, Collin M, Cohen-Aubart F, Vaglio A, Durham BH, et al. Erdheim-Chester disease: consensus recommendations for evaluation, diagnosis, and treatment in the molecular era. Blood. 2020;135:1929–45.
12. Toro Galván S, Planas Vilaseca A, Michalopoulou Alevras T, Torres Díaz A, Suárez Balaguer J, Villabona Artero C. Endocrine changes in histiocytosis of the hypothalamic-pituitary axis. Endocrinol Nutr. 2015;62:72–9.

María José Vallejo Herrera[a,*], Francisco José Sánchez Torralvo[a], Verónica Vallejo Herrera[b], Gabriel Olveira Fuster[a], Iván Pérez de Pedro[c]

[a] *UGC Endocrinología y Nutrición, Hospital Regional Universitario de Málaga, Málaga, Spain*
[b] *UGC Radiodiagnóstico, Hospital Regional Universitario de Málaga, Spain*
[c] *UGC Medicina Interna, Hospital Regional Universitario de Málaga, Spain*

* Corresponding author.
E-mail address: mariajosevallejoherrera@gmail.com (M.J. Vallejo Herrera).

Dyslipidaemia in patients with haematology/oncology diseases☆

Dislipemia en pacientes con enfermedades onco-hematológicas

The prevalence of neoplastic diseases, as well as survival in patients with these diseases, have increased in recent years.[1] The rise in life expectancy has been seen to be linked to a rise in the prevalence of morbidity and mortality due to cardiovascular diseases. Furthermore, a clear relationship between cardiovascular health and development of neoplastic diseases has been observed.[2]

Patients with cancer are also at higher risk of developing cardiovascular disease. This may be linked to concomitant risk factors for developing cancer and cardiovascular disease (CVD) (tobacco use) or due to treatments for different types of cancer (anthracyclines). Specifically, patients with lung cancer have a CVD prevalence of 43%, while patients with kidney or colon cancer have a CVD prevalence exceeding 20%. Patients with haematological neoplasms have a CVD prevalence of 33%, a prevalence of peripheral arterial disease of 20%, a prevalence of coronary disease of 16% and a prevalence of cerebrovascular disease and heart failure of 9%.[3]

With respect to these neoplasms, the increase in survival in some diseases has been very significant. The 10-year survival prognosis in chronic myeloid leukaemia has improved by 40% since the pre-tyrosine kinase inhibitor (TKI) era, and now is similar to that of the general population.[4] In addition, patients who undergo haematopoietic stem cell transplantation (HSCT) for various haematological diseases have seen

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their survival increase by 10% each decade, up to 90% five years after transplantation and 80% 10 years thereafter at present.[5] In these cases, CVD has been a leading cause of morbidity and mortality.[5,6]

There is a clear relationship between the presence of cardiovascular risk factors (CVRFs) and the development of CVD, which is also seen in the population with cancer. Furthermore, in these patients in particular, many chemotherapy treatments result in CVD either directly or through the onset of CVRFs.

In the management of CVRFs in patients with cancer, certain characteristics are to be taken into account: pathophysiological mechanisms of CVRFs, clinical frailty and, above all, a high risk of drug-drug interactions, including chemotherapy agents and immunosuppressants.

Below, we report three clinical cases of patients with a history of haematological neoplastic diseases and dyslipidaemia to illustrate the complexity of these patients' follow-up and treatment. In all three cases, laboratory tests with a lipid profile were repeated after three and six months, and treatment outcomes were verified three months after they were started.

Case 1

A 35-year-old man had a disease history of chronic myeloid leukaemia diagnosed in January 2017. He was initially treated with dasatinib 100 mg every 24 h, then switched to nilotinib 300 mg in April 2019 due to an incomplete cytogenetic response.

He came in with dyslipidaemia, with total cholesterol (TC) 246 mg/dl, high-density lipoprotein cholesterol (HDL-C) 49 mg/dl, low-density lipoprotein cholesterol (LDL-C) 185 mg/dl and triglycerides (TGs) 131 mg/dl. In his medical history, he denied signs and symptoms of ischaemic heart disease and peripheral arterial disease, and an electrocardiogram and ankle–brachial pressure index showed normal results. He weighed 80 kg and was 1.81 m tall. In his lipid profile prior to treatment, he had TC 179 mg/dl, HDL-C 46 mg/dl, LDL-C 110 mg/dl and TGs 115 mg/dl.

He was started on treatment with hygiene and dietary measures as well as rosuvastatin 10 mg; his lipid profile improved to TC 175 mg/dl, HDL-C 65 mg/dl, LDL-C 96 mg/dl and TGs 71 mg/dl.

Case 2

A 33-year-old woman had a disease history of severe bone marrow aplasia treated with allogeneic HSCT from a human leukocyte antigen (HLA)-identical sibling. She received induction therapy with a CPM-ATG (cyclophosphamide and antithymocyte globulin) protocol. She developed MAGIC II gastric graft-versus-host disease (GVHD) treated with ciclosporin 150 mg daily, beclometasone 6 mg daily and sirolimus 2 mg daily. She also developed iatrogenic hypothyroidism after radioactive iodine therapy for hyperthyroidism, managed with levothyroxine 88 mcg.

She came in on day + 82 of the post-transplant period with hypertension and mixed dyslipidaemia. She weighed 86.5 kg and was 1.78 m tall. Her hypertension was managed with olmesartan 40/hydrochlorothiazide 12.5 mg 1 pill in the morning. She had a lipid profile with TC 276 mg/dl, HDL-C 35 mg/dl, LDL-C 150 mg/dl and TGs 1,242 mg/dl. She was prescribed a low-fat diet and started on treatment with pitavastatin 4 mg and fenofibrate 160 mg daily, achieving improvement in her lipid profile with TC 247, HDL-C 63, LDL-C 121 and TGs 353. In subsequent follow-up, after her sirolimus dose was lowered, her TG levels dropped to 234 mg/dl.

Case 3

A 55-year-old woman with a disease history of treated B-cell chronic lymphocytic leukaemia who underwent allogeneic HSCT. She had previously received first-line treatment with oral fludarabine alone for three cycles and second-line treatment with fludarabine/rituximab for three cycles. She received a conditioning regimen with a protocol with fludarabine and cyclophosphamide (FLUCY). She subsequently developed chronic mucosal and fascial GVHD, treated with beclometasone, sirolimus and topical tacrolimus. She also developed grade G3a2 chronic kidney disease due to nephroangiosclerosis and prior use of systemic tacrolimus.

After starting immunosuppressive therapy, the patient developed refractory hypertension and hypercholesterolaemia. The former was treated with a combination of olmesartan 40/amlodipine 10/hydrochlorothiazide 12.5 mg, with good management of blood pressure levels. As for her dyslipidaemia, the patient did not tolerate treatment with various statins and ezetimibe: she experienced muscle pain and hypertransaminasaemia with atorvastatin 40 mg, rosuvastatin 10 mg and ezetimibe 10 mg, and did not achieve her treatment objectives with pitavastatin 4 mg.

From a cardiovascular point of view, she showed no symptoms during consultation. She weighed 64 kg and was 1.70 m tall. Recent testing showed a lipid profile with TC 276 mg/dl, HDL-C 81 mg/dl, LDL-C 158 mg/dl and TGs 187 mg/dl.

Due to her high cardiovascular risk, a decision was made to start treatment with alirocumab 150 mg with one subcutaneous injection every two weeks. With this treatment and sustained 4-mg doses of pitavastatin, her lipid profile improved to TC 224 mg/dl, HDL-C 87 mg/dl, LDL-C 110 mg/dl and TGs 133 mg/dl.

Discussion

Treating dyslipidaemia in patients with haematological neoplasms can represent a challenge. Many drugs used as chemotherapy agents or immunosuppressants can cause metabolic and cardiovascular toxicity, with patients developing dyslipidaemia and other conditions and facing increased cardiovascular risk (Table 1).

The prognosis for chronic myeloid leukaemia (CML) changed radically in 2001 following the introduction of TKIs; imatinib, dasatinib, nilotinib, bosutinib and ponatinib are the TKIs that are currently available. Dasatinib, nilotinib and ponatinib sometimes cause metabolic and cardiovascular toxicity, while bosutinib and ponatinib are known to cause CVD. Nilotinib specifically has been linked to arterial vascular disease (ischaemic heart disease, cerebrovascular disease and peripheral arterial disease) as well as hyperglycaemia and hyperlipidaemia.[7] Although the mechanism by

Table 1 Metabolic and cardiovascular side effects induced by chemotherapy and immunosuppressive therapy.

Drug	Type	Main indications	Therapeutic target/Mechanism of action	Metabolic and cardiovascular effects
TYROSINE KINASE INHIBITORS				
Dasatinib	BCR-ABL TKI	ALL, Ph + CML Off-label: GIST	Selective BCR-ABL kinase inh. SRC family (SRC; LKC, YES, FYN), c-KIT, EPHA2 and PDGFR-® inh.	Pleuropericardial effusion Pulmonary hypertension Myocardial conduction abnormalities
Imatinib	BCR-ABL TKI	Ph + CML, Ph + ALL, GIST, severe systemic mastocytosis.	BCR-ABL inh.	Peripheral oedema
Lenvatinib	VEGF inh. TKI	Unresectable HCC. Advanced kidney ca. MET differentiated thyroid ca.	VEGF multi-targeted TKI: VEGFR-1, VEGFR-2, VEGFR-3, FGF, FGFR-1, FGFR-2, FGFR-3, FGFR-4, PDGFR-(, KIT and RET.	Hypercholesterolaemia HTN QT interval prolongation. HF. Arterial thromboembolism.
Nilotinib	BCR-ABL TKI	Ph + CML Off-label: Ph + ALL, GIST.	Selective BCR-ABL kinase, c-KIT and PDGFR inh.	Hypercholesterolaemia HTN Hyperglycaemia PAD. IHD. Stroke. QT interval prolongation
Ponatinib	BCR-ABL TKI	ALL, CML	BCR-ABL TKI pan-inhibition (VEGFR, FGFR, PDGFR, EPG, SRC, KIT, RET, TIE2 and FLT3)	HTN Hyperglycaemia PAD. CVA. IHD. Arterial occlusive disease
Ruxolitinib	IJC TKI	Myelofibrosis. Polycythaemia vera. Acute GVHD.	Selective inhibition of JAK1 and JAK2	Hypercholesterolaemia, hypertriglyceridaemia Hypertension
OTHER CHEMOTHERAPY AND IMMUNOSUPPRESSIVE AGENTS				
Glucocorticoids	Corticosteroids	–	–	(Dose >10 mg PRED) Hypertriglyceridaemia. Hypercholesterolaemia Diabetes Hypertension Fluid retention. Premature atherosclerotic disease
mTOR KINASE INHIBITORS				
Sirolimus	IS. mTOR kinase inh.	GVHD, heart transplantation, lung transplantation	Inhibits T lymphocyte activation and proliferation in response to antigen stimulation and stimulation with cytokines and inhibits antibody production. Binds to FKBP-12, an intracellular protein, to form an immunosuppressant complex that inhibits the regulatory kinase mTOR (a mechanical target of rapamycin).	Hypertriglyceridaemia. Hypercholesterolaemia HTN Diabetes mellitus DVT. PTE
Tacrolimus	IS. Calcineurin inh.	Kidney rejection, heart rejection, liver rejection. Off-label: GVHD	Suppresses cellular immunity (inhibits T lymphocyte activation) by binding to an intracellular protein, FKBP-12, and complexes with calcineurin-dependent proteins to inhibit calcineurin phosphatase activity.	HTN Heart failure. Arrhythmia

Table 1 (*Continued*)

Drug	Type	Main indications	Therapeutic target/Mechanism of action	Metabolic and cardiovascular effects
Ciclosporin	Calcineurin inhibitor	Tx rejection prophylaxis, RA. Off-label: GVHD, lupus nephritis	Inhibits interleukin II production and release and inhibits interleukin II-induced activation of resting T lymphocytes.	Hypercholesterolaemia. Hypertriglyceridaemia HTN Hypoglycaemia. Hyperglycaemia
RADIATION-RELATED TOXICITY				
Thoracic and mediastinal radiotherapy				Whole-body RT: DM, DL ≥60 Gy: microvascular and macrovascular endothelial damage. Accelerated atherosclerosis. Heart valve disease. Pericardial disease (constrictive/exudative pericarditis). REF heart failure (acute or chronic)

ABL, ABL proto-oncogene; ALL, acute lymphoblastic leukaemia; Ca, cancer; CML, chronic myeloid leukaemia; CVA, cerebrovascular accident; DL, dyslipidaemia; DM, diabetes mellitus; DVT, deep vein thrombosis; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; FLT3, FMS-like tyrosine kinase 3; GIST, gastrointestinal stromal tumour; GVHD, graft-versus-host disease; Gy, Gray; HCC, hepatocellular carcinoma; HF, heart failure; HTN, hypertension; IHD, ischaemic heart disease; Inh, inhibitor; IS, immunosuppressant; JAK, janus kinase; KIT, KIT tyrosine kinase protein; MET, metastatic; PAD, peripheral arterial disease; PDGFR, platelet-derived growth factor receptor; PRED, prednisone; PTE, pulmonary thromboembolism; RA, rheumatoid arthritis; REF, reduced ejection fraction; RET, glial cell line-derived neurotrophic receptor factor; RT, radiotherapy; SRC, SRC proto-oncogene non-receptor tyrosine kinase; TIE2, TEK receptor tyrosine kinase; TKI, tyrosine kinase inhibitor; Tx, transplantation; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

which elevation of LDL-C particles occurs is unknown, it was recently found that systemic inflammation due to increased oxidised LDL-C particles could additionally cause a pro-oxidative, pro-inflammatory state that would contribute to CVD risk.[8] Another particular characteristic of these patients with dyslipidaemia treated with nilotinib (as seen in Case 1) is that treatment with statins metabolised by cytochrome P450 CYP 3A4 should be avoided, due to the increased risk of toxicity.

Regarding immunosuppressive therapy used in HSCT, sirolimus, a mammalian target of rapamycin (mTOR) inhibitor, is known to cause lipid metabolism abnormalities in 40%–75% of treated subjects, mainly hypertriglyceridaemia, as in Case 2. In some cases, TG levels may be so high that they tend to cause acute pancreatitis. Metabolic abnormalities consist of increased lipolysis, decreased adipogenesis and decreased LDL-C blood clearance. Paradoxically, in animal models, sirolimus has been found to reduce the progression of atherosclerosis, thus improving endothelial function, inhibiting proliferation of smooth muscle cells, decreasing macrophage content in plaque and reducing monocyte recruitment.[9]

In the third case, the drug involved was ciclosporin, a calcineurin inhibitor, which interferes with LDL-C binding to the LDL receptor, with a decrease in LDL clearance. There may also be other additional mechanisms such as synthesis of ciclosporin-reducing bile acids, which lead to LDL receptor down-regulation and reduce cholesterol elimination. There may be synergistic effects in patients who are also on treatment with corticosteroids. Other calcineurin inhibitors, such as tacrolimus, cause dyslipidaemia by the same mechanism, although the answer to the question of why lipid levels are lower is unknown.[10]

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are drugs that have gained importance in recent years in the treatment of hypercholesterolaemia. Their main uses are in patients in whom metabolic targets are not achieved despite maximum tolerated doses of statins and/or ezetimibe. They have proven to be powerful reducers of LDL-C levels with few adverse effects (16). While their use is widely standardised in patients in secondary prevention therapy and in diseases such as the various forms of familial hypercholesterolaemia, there are no data on their use in HSCT. However, given these drugs' safe mechanism of action, there are no contraindications to their use in this population.

Conclusions

In patients with cancer, dyslipidaemia should be treated according to the instructions of the different clinical guidelines, with strict monitoring of lipid levels. It should be borne in mind that many drugs used to treat neoplasms and manage rejection in transplant recipients can cause dyslipidaemia. Furthermore, potential drug-drug interactions should be avoided in these subjects, as they are often polymedicated. PCSK9 inhibitors are safe drugs that represent an option in the treatment of dyslipidaemia.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References

1. Bluethmann SM, Mariotto AB, Rowland JH. Anticipating the 'Silver Tsunami': prevalence trajectories and co-morbidity burden among older cancer survivors in the United States. Cancer Epidemiol Biomarkers Prev. 2016;25(7):1029–36.
2. Rasmussen-Torvik LJ, Shay CM, Abramson JG, Friedrich CA, Nettleton JA, Prizment AE, et al. Ideal cardiovascular health is inversely associated with incident cancer: the atherosclerosis risk in communities study. Circulation. 2013;127(12):1270–5.
3. Al-Kindi SG, Oliveira GH. Prevalence of preexisting cardiovascular disease in patients with different types of cancer: the unmet need for onco-cardiology. Mayo Clin Proc. 2016;91(1):81–3.
4. Shallis RM, Wang R, Davidoff A, Ma X, Podoltsev NA, Zeidan AM. Epidemiology of the classical myeloproliferative neoplasms/the four corners of an expansive and complex map. Blood Reviews. 2020;42:100706.
5. Bhatia S, Francisco L, Carter A, Sun C-L, Baker KS, Gurney JG, et al. Late mortality after allogeneic hematopoietic cell transplantation and functional status of long-term survivors/report from the Bone Marrow Transplant Survivor Study. Blood. 2007;110:3784–92.
6. Douxfils J. Association between BCR-ABL tyrosine kinase inhibitors for chronic myeloid leukemia and cardiovascular events, major molecular response, and overall survival. A systematic review and meta-analysis. JAMA Oncol. 2016;2(5):625–32.
7. Damrongwatanasuk R. Cardiovascular complications of targeted therapies for chronic myeloid leukemia. Curr Treat Options Cardio Med. 2017;19:24.
8. Gustafson D, Fish JE, Lipton JG, Angel N. Mechanism of cardiovascular toxicity of BCR-ABL1 tyrosine kinase inhibitors in chronic myelogenous leukemia. Curr Hematol Malig Rep. 2020;15(1):20–30.
9. Kurdi A, Martinet W, De Meyer GRY. mTOR Inhibition and cardiovascular diseases: dyslipidemia and atherosclerosis. Transplantation. 2018;102 2S Suppl 1:S44–6.
10. Chakkera HA, Sharif A, Kaplan B. Negative cardiovascular consequences of small molecule immunosuppressants. Clin Pharmacol Ther. 2017;102(2):269–76.

Ricardo Roa-Chamorro[a,*], Lucía Torres-Quintero[b], Pablo González-Bustos[a], José Manuel Puerta-Puerta[c], Fernando Jaén-Águila[a], Juan Diego Mediavilla-García[a]

[a] *Unidad de Hipertensión y Riesgo Vascular, Servicio de Medicina Interna, Hospital Universitario Virgen de las Nieves, Granada, Spain*
[b] *Cardiología. Hospital Universitario Virgen de las Nieves, Granada, Spain*
[c] *Hematología. Hospital Universitario Virgen de las Nieves, Granada, Spain*

* Corresponding author.
E-mail address: ricardo.roa.sspa@juntadeandalucia.es (R. Roa-Chamorro).

Prevalence of gestational diabetes with a 2-step strategy and cut-off values from the 1979 *National Diabetes Data Group*. Are we applying the best strategy for our patients?☆

Prevalencia de diabetes gestacional con una estrategia de 2 pasos y valores de corte del *National Diabetes Data Group* de 1979. ¿Estamos utilizando la mejor estrategia para nuestras pacientes?

Gestational diabetes (GD) is diabetes first diagnosed during the second or third trimester of pregnancy not clearly due to the presence of pre-existing diabetes.[1] The prevalence of GD varies widely depending on diagnostic criteria, ethnicity and prevalence of type 2 diabetes in the population.[2,3] There is currently no consensus among scientific associations regarding the diagnostic criteria for GD, meaning that different strategies coexist: (1) a one-step strategy, as proposed by the International Association of Diabetes and Pregnancy Study Groups; and (2) a two-step strategy with cut-off points from the National Diabetes Data Group (NDDG) or from Carpenter and Coustan. Regardless of the strategy used, the diagnosis of GD has significant repercussions for mothers and their newborns.[4] A multicentre study conducted in Spain on the possible impact of applying the Carpenter and Coustan criteria confirmed the high prevalence of GD according to the c̈lassicN̈DDG criteria, which would further increase with the application of the Carpenter and Coustan criteria.[5] Application of the International Association of Diabetes and Pregnancy Study Groups criteria in our setting would further increase the prevalence of GD, but could be associated with better pregnancy outcomes and ultimately a reduction in direct costs.[6–8] For this reason, according to the recommendations of the Grupo Español de Diabetes y Embarazo [Spanish Diabetes and Pregnancy Group],[9] our centre uses a two-step strategy with NDDG cut-off points.

The working hypothesis was that, in our setting, the complexity of the (two-step) method and the established (NDDG) cut-off points could reduce the prevalence of GD compared to the expected prevalence despite the significant resources required to implement it. For this reason, we designed a

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