Caso clínico

Hipoparatireoidismo e hipertensão pulmonar como apresentação clínica de linfoma folicular

Follicular Lymphoma Presenting with Hypoparathyroidism and Pulmonary Hypertension

Autores:
Sara Coelho, Helena Magalhães, Jorge Correia, Patrícia Lourenço, José Paulo Araújo, Paulo Bettencourt

Afiliação:
Sara Coelho, Helena Magalhães
Serviço de Medicina Interna, Centro Hospitalar São João, E.P.E., Porto, Portugal
Serviço de Oncologia Médica, Instituto Português de Oncologia, E.P.E, Porto, Portugal

Jorge Correia, Patrícia Lourenço
Serviço de Medicina Interna, Centro Hospitalar São João, E.P.E., Porto, Portugal

José Paulo Araújo, Paulo Bettencourt
Serviço de Medicina Interna, Centro Hospitalar São João, E.P.E., Porto, Portugal
Faculdade de Medicina da Universidade do Porto, Porto, Portugal

Conflitos de interesse:
Sem conflitos de interesse.

Financiamento:
Não se aplica.

Autor para correspondência:
Sara Coelho
Morada: Serviço de Medicina Interna, Hospital S. João
Alameda Professor Hernâni Monteiro, 4202-451 PORTO
Email: u011793@hsjoao.min-saude.pt

Resumo

Uma mulher de 79 anos foi internada para estudo de hipertensão pulmonar sugerida em ecocardiograma. Apresentava associadamente uma hipocalcemia grave com níveis de hormona paratireóide inapropriadamente diminuídos. A tomografia computorizada mostrou uma adenopatia paratraqueal (46x32 mm) e múltiplas adenopatias abdominais, que após biópsia cirúrgica demonstraram corresponder a um linfoma folicular. Não foram identificadas outras causas que justificassem a hipertensão pulmonar, que foi por isso atribuída ao distúrbio linfoproliferativo (hipertensão pulmonar tipo 5). O hipoparatireoidismo foi considerado secundário a infiltração das paratireóides.

Palavras-chave: Linfoma folicular, hipertensão pulmonar, hipocalcemia, hipoparatireoidismo

Summary

A 79-year-old woman was admitted to our hospital so we could study the aetiology of pulmonary hypertension that had been suggested in an echocardiogram. She also had severe hypocalcaemia with an inappropriately low parathyroid hormone level. Computed tomography showed a paratracheal (46×32 mm) adenopathy and multiple abdominal adenopathies, which were surgically biopsied and corresponded to follicular lymphoma. No other causes were found for the pulmonary hypertension that was considered to be associated with lymphoproliferative disease – pulmonary hypertension type 5. Hypoparathyroidism was considered secondary to parathyroid infiltration.

Keywords: *Follicular lymphoma, pulmonary hypertension, hypocalcaemia, hypoparathyroidism*

Introduction

Follicular lymphoma (FL) is the second most common lymphoma in the United States and Western Europe, and the most indolent form of non-Hodgkin lymphoma.[1] The median diagnosis age is 60–65 years old and there is a small preponderance in women.[2] The disease is characterized mainly by nodal and bone marrow involvement and B symptoms are present in only 20% of patients.[3] Genetically, t(14;18)(q32;q21) chromosome translocation represents the molecular hallmark of FL.[4]

We report a case of FL presenting multiple lymph node involvement, pulmonary hypertension (PH) and hypoparathyroidism.

Case report

A 79-year-old woman was referred to our hospital with recently diagnosed PH. The transthoracic echocardiography revealed severe dilation of right heart chambers, right ventricle volume overload and severe tricuspid insufficiency. The left chambers were only mildly affected. Right and left ventricular systolic function was normal. The patient had exertion dyspnoea, loss of appetite, nausea, and circum-oral and extremities paresthesias for 1 year, and generalized pruritus for the last 2 months. She had no weight-loss, fever, orthopnoea or paroxysmal nocturnal dyspnoea. She had a recently diagnosed atrial fibrillation, a past medical history of arterial hypertension, and an idiopathic pericarditis 2 years before. She had no history of thrombo-embolic events, and no pulmonary, rheumatologic, auto-immune or neoplastic diseases. She had no past history of cigarette smoking and no contact with environmental toxins. There was no history of travelling to developing countries.

Her body mass index was 25.8 Kg/m^2; blood pressure was 110/68 mm Hg; and heart rate was 68 beats per minute. She was eupnoeic at rest with an oxygen saturation of 97% while breathing room air, and was apyretic. She had an Eastern Cooperative Oncology Group Performance Status of 3 and bilateral sub-conjunctival haemorrhages. She was mildly icteric and had itchy lesions throughout her body, mainly in thorax and axillae. The second heart sound was increased. She had a positive jugular vein turgor and jugular hepatic reflux, and her hepatic border was palpable, regular and painless. Trousseau and Chvostek signs were positive.

She had a haemoglobin of 11.7 g/dL, mild elevation of hepatic cholestasis markers gamma-glutamyl transferase 269 U/L, alkaline phosphatase 107 U/L, total bilirubin levels of 0.91 mg/dL with normal aspartate aminotransferase (18 U/L) and alanine aminotransferase (43 U/L). Her plasma urea was 22 mg/dL and creatinine 0.79 mg/dL. She had severe hypocalcaemia (0.94 mEq/L) with a phosphataemia of 4.5 mg/dL, associated with inappropriately low parathyroid hormone (PTH) level (12.2 pg/mL) and vitamin D deficiency (4 ng/mL). She also had mild hypomagnesemia (1.07 mEq/L), hypokalaemia (3.2 mEq/L) and elevated brain-natriuretic peptide (828.6 pg/mL). Phosphocalcium and electrolytic disturbances were corrected.

An abdominal ultrasound showed inferior vena cava supra-hepatic veins dilation without hepatomegaly. She had normal thyroid function and serum immunology, and HIV testing was negative. The cervical-thoracic-abdominal-pelvic computed tomography angiography (Fig. 1) demonstrated multiple adenopathies: one in the paratracheal region (46×32×26 mm), a conglomerate adenopathy at the mesenteric root with 36×19 mm, and a lumbosacral adenopathy with 17×22×12 mm. There was no splenic or liver involvement. There were no signs of thrombotic events in the pulmonary vessels. There were no pleural or pericardial effusions nor calcifications.

Laparoscopic surgery was performed for excisional biopsy of the conglomerate mesenteric adenopathy, and the histological examination showed a grade 2 FL (Figs. 2–4).

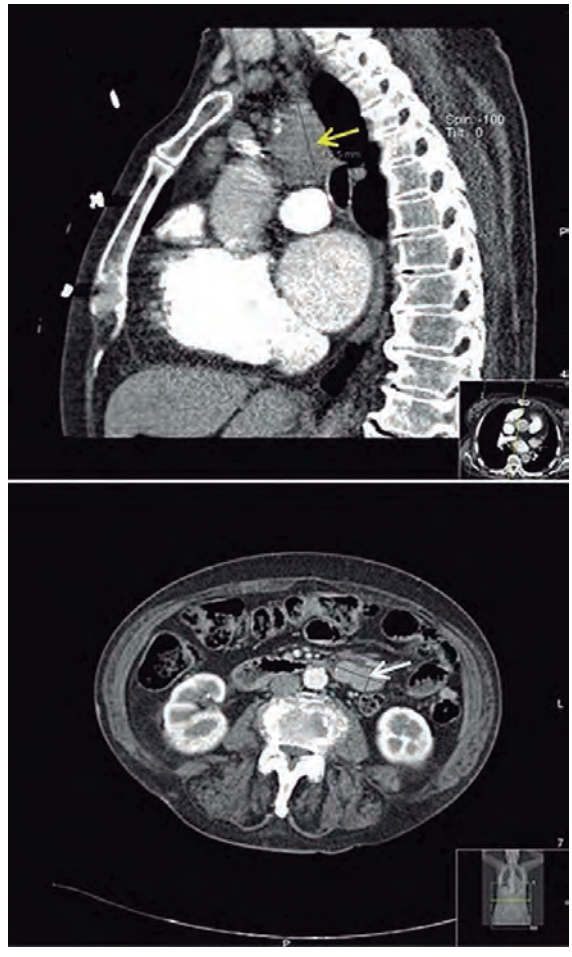

Figure 1. Computed tomography revealing a paratracheal adenopathy with 46×32×26 mm (yellow arrow) and a mesenteric root conglomerate adenopathy with 36×19 mm (white arrow).

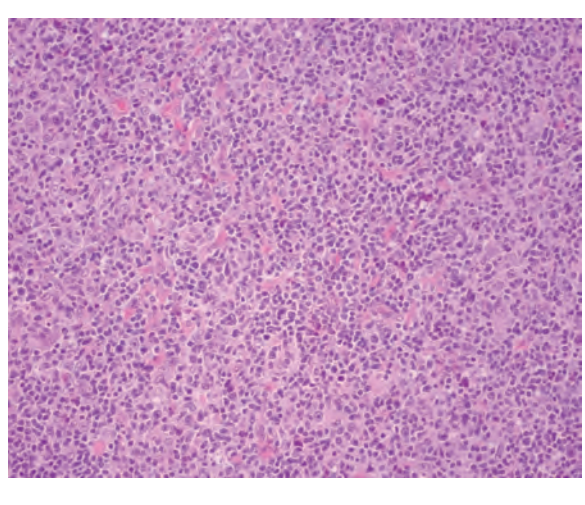

Figure 2. Hematoxylin and eosin staining: follicular lymphoma grade 2 (6–15 blasts/high power field).

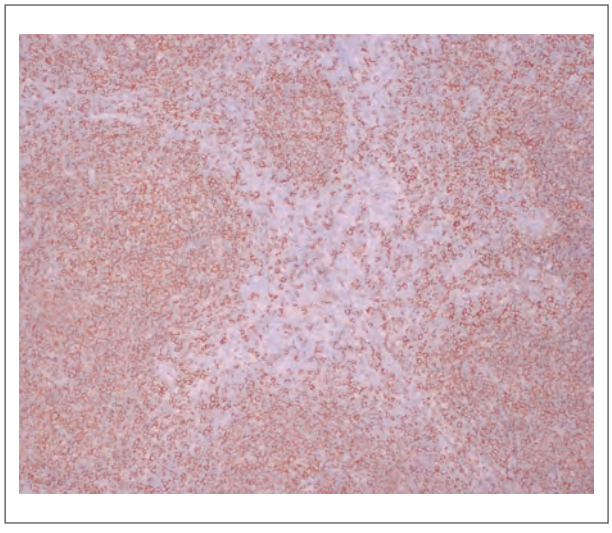

Figure 3. CD20 staining in histological tissue sections: the lymphoid population was positive for CD20.

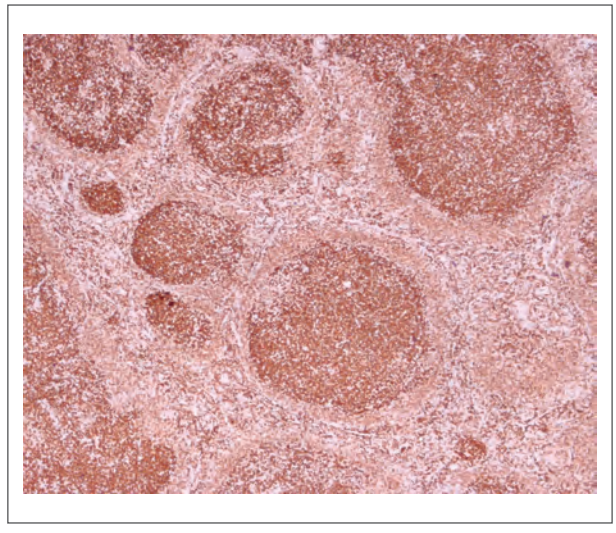

Figure 4. Immunohistochemistry to Bcl-2: there are inappropriately high levels of Bcl-2 expression in follicle centre B cells.

There was no medullary involvement. The patient's uric acid level was 7.7 mg/dL and β2-microglobulin and lactate dehydrogenase were elevated (4923 µg/L and 770 U/L, respectively). The lymphoma was classified as stage IIIb based on the Ann Arbor Classification, and was considered high risk based on the Follicular Lymphoma International Prognostic Index.[5]

FL was assumed to be the cause of the PH – group 5 of PH according to the WHO classification.[6] It was considered that hypocalcaemia resulted from parathyroid infiltration by the neoplastic adjacent adenopathies.

A 'watch and wait' strategy was chosen based on the patient's comorbidities, age and preferences, although the presence of symptoms were related to the disease. Currently, 10 months have passed since the diagnosis of FL and the patient is clinically stable in New York Heart Association class II and with no evidence of disease progression in serial computed tomographies. Calcium and phosphate levels are normal with cholecalciferol and calcium supplements. The patient is anticoagulated with warfarin and is on a loop diuretic (furosemide 40 mg/day).

Discussion

FL is an indolent form of non-Hodgkin lymphoma and the majority of patients are diagnosed when the disease is already at an advanced stage. Constitutional symptoms are not frequent at presentation.[7]

We report a rare case of FL presenting with atypical clinical features: unexplained PH and severe hypocalcaemia. The association of lymphomas with either PH or hypocalcaemia is rare.

PH is defined by a mean pulmonary arterial pressure >25 mm Hg at rest; diagnosis can be suggested by echocardiography. However, the gold standard is assessment by right heart catheterization, though the latter was not performed in our patient.[6,8] The classification of PH consists of five major groups based on PH aetiology; group 5 comprises miscellaneous causes of PH with unclear and/or multifactorial mechanisms, including neoplasias.[6] The two most commonly proposed mechanisms for the aetiology of neoplasia-associated PH are pulmonary tumour thrombotic-microangiopathy and pulmonary tumour embolism.[9] There are few case reports of lymphoma-associated PH and most are intravascular lymphomas, a rare type of diffuse large B cell lymphoma.[10-13] No case of PH associated with FL has been previously reported.

Although hypercalcaemia due to neoplasia is more frequent, hypocalcaemia can also occur. Multiple factors can contribute to hypocalcaemia: hypoalbuminaemia, hypomagnesaemia, vitamin D deficiency, renal failure, tumour lysis syndrome, infection or drug effects, among others.[14] Infiltrative parathyroid disease is a rare cause of hypocalcaemia, which has already been described for various neoplasias, especially breast and prostate adenocarcinomas.[15] In our patient, the PTH level was inappropriately low, and was likely explained by a diffuse infiltrating neoplastic process due to FL.

For the majority of patients with stage III disease, current FL guidelines suggest that therapy should only be initiated if the patient is symptomatic, or when there is haematopoietic impairment, bulky disease, vital organ compression, ascites, pleural effusion or rapid lymphoma progression.[5,16] There are anecdotal reports describing PH symptoms regression with lymphoma-oriented therapy.[10] In this specific case, rituximab or a chemo-immunotherapy strategy would be possible choices.[5]

Neoplastic diseases should be kept in mind when studying otherwise unexplained PH or primary hypoparathyroidism.

References

1. Gribben JG. How I treat indolent lymphoma. Blood. 2007;109(11):4617-4626.
2. Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. J Clin Oncol. 1998;16(8):2780-2795.
3. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. Blood. 2011;117(19):5019-5032.
4. Ott G, Rosenwald A. Molecular pathogenesis of follicular lymphoma. Haematologica. 2008;93(12):1773-1776.
5. Dreyling M, Ghielmini M, Marcus R, Salles G, Vitolo U, Ladetto M. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25 (Suppl 3):iii76-82.
6. Galiè N, Hoeper MM, Humbert M, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension – The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and of the European Respiratory Society (ERS) Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;77(1):67-119.
7. Freedman A. Follicular Lymphoma 2014 update on diagnosis and management. Am J Hematol. 2014;89(4):429-436.
8. Baldi F, Fuso L, Arrighi E, Valente S. Optimal management of pulmonary arterial hypertension: prognostic indicators to determine treatment course. Ther Clin Risk Manag. 2014;10:825–839.
9. Hotta M, Ishida M, Kojima F, Iwai Y, Okabe H. Pulmonary tumor thrombotic microangiopathy caused by lung adenocarcinoma: case report with review of literature. Oncol Lett. 2011;2(3):435-437.
10. Liu C, Lai N, Zhou Y, Li S, Chen R, Zhang N. Intravascular large B-cell lymphoma confirmed by lung biopsy. Int J Clin Exp Patho. 2014;7(9):6301-6306.
11. Watanabe S, Takato H, Waseda Y, et al. Pulmonary T-cell lymphoma with pulmonary arterial hypertension. Intern Med. 2011;50(16):1733-1736.
12. Exline M, Magro C, Lin T, Sood N. Pulmonary hypertension in Hodgkin's disease. Thorax. 2007;62(4):371.
13. Blaquière G, Bolo M, Inamo J, et al. Primary pulmonary hypertension associated with HTLV-I retrovirus infection at the adult T-cell leukemia lymphoma stage. Presse Med. 2004;33(5):316-317.
14. Michels TC, Kelly KM. Parathyroid disorders. Am Fam Physician. 2013;88(4):249-257.
15. Bergkamp FJ, Berkel AM, Linden PW, Gorgels JP. Unexpected prolonged extreme hypocalcaemia and an inadequate PTH response in a patient with metastatic breast carcinoma. Neth J Med. 2003;61(11):371-375.
16. Federico M, Vitolo U, Zinzani PL, et al. Prognosis of follicular lymphoma: a predictive model based on a retrospective analysis of 987 cases. Intergruppo Italiano Linfomi. Blood. 2000;95(3):783-789.