The Course of an Autosomal Dominant Polycystic Kidney Disease: Rare Association with Waldenström Macroglobulinemia and other Co-occurrences

O Percurso de uma Doença Poliquística Renal Autossómica Dominante: Associação Rara com Macroglobulinemia de Waldenström e outras Coocorrências

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Abstract:

We present a case of a 50-year-old female, known to have a history of autosomal dominant polycystic kidney disease (ADPKD) and controlled hypertension, who was referred for polycystic liver. Her family history is remarkable for her father, who received a renal transplant in the setting of ADPKD. The patient remained under regular follow-up with normal renal and hepatic function. She developed recurrent episodes of pain in the upper abdomen, malnutrition and cyst infection. At this point, she had signs of hepatic venous outflow obstruction and imaging showed massive liver enlargement. The patient was proposed for a liver transplant. A decade after ADPKD was identified, she had been diagnosed with Waldenström macroglobulinemia (WM). Hematological malignancies have rarely been described in coexistence with ADPKD. There is one such reported case with multiple myeloma. However, in our search, we have not found any case of ADPKD-associated WM. This association should prompt thorough and frequent monitoring.

Keywords: Polycystic Kidney, Autosomal Dominant; Polycystic Liver Disease; Waldenström Macroglobulinemia.

Resumo:

Relatamos o caso de uma doente de 50 anos, com antecedentes de doença poliquística renal autossómica dominante (DPRAD) e hipertensão controlada, que foi referenciada por fígado poliquístico. A sua história familiar é positiva para DRPAD, com pai transplantado renal neste contexto. A doente permaneceu em seguimento regular, mantendo função renal e hepática normais. Desenvolveu episódios recorrentes de dor no abdómen superior, malnutrição e infeção de quistos. Nesta fase, apresentava sinais compatíveis com obstrução do fluxo venoso hepático e os exames de imagem mostraram aumento exuberante do fígado. A doente foi proposta para transplante hepático. Uma década após a identificação da DRPAD, foi diagnosticada com macroglobulinemia de Waldenström (MW). As neoplasias hematológicas têm sido raramente descritas em coexistência com DRPAD, existindo um caso relatado com mieloma múltiplo. Contudo, na nossa pesquisa não encontrámos nenhum caso de MW associada à DRPAD. Esta associação deve motivar uma vigilância cuidada e regular.

Palavras-chave: Doença Hepática Poliquística; Doença Poliquística Renal Autossómica Dominante; Macroglobulinemia de Waldenström.

Learning Points

1. ADPKD has a systemic nature with several possible complications and associations throughout the course of the disease
2. Rare association of plasma cell dyscrasias and ADPKD may occur
3. Thus, an altered blood count in the setting of ADPKD with various complications should prompt further evaluation

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disorder in adults, with a prevalence of 1:1000 to 1:2500.[1] It is characterized by progressive development and growth of renal cysts that ultimately lead to end-stage renal disease in around 50% of patients by the sixth decade of life.[2] Patients usually remain symptom-free until the third to fourth decades of life, when compression symptoms arise due to enlarged cysts.[3] This disease has a systemic nature as it presents with variable renal and extrarenal manifestations.[2] Renal manifestations include hypertension, pain syndrome due to compression or cyst complication (hemorrhage, infection, rupture), urolithiasis, urinary tract infections (UTI) and progressive chronic kidney disease (CKD).[2] Renal cell carcinoma is an infrequent late term complication.[2] Extrarenal manifestations can

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be divided into cystic (cysts in different organs) and non-cystic (such as intracranial aneurysms, cardiac involvement and valve lesions, colonic diverticula, abdominal hernias) complications.[2] Polycystic liver disease (PLD) is the most frequent extrarenal manifestation and in the majority of cases is not associated with symptoms or liver dysfunction.[2,4] Patients with moderate and severe PLD have higher risk of symptoms and complications.[4–6] The main risk factors for progression of PLD include female gender, multiple pregnancies and prolonged use of estrogens.[4,5]

Waldenström macroglobulinemia (WM) is a rare and indolent B-cell lymphoma characterized by the infiltration of the bone marrow by clonal lymphoplasmacytic cells that produce monoclonal IgM.[7] Fatigue related to normocytic anemia is the most frequent presenting symptom, although other manifestations may include fever, night sweats, weight loss, hepatomegaly, splenomegaly, lymphadenopathy, cytopenias, and rarely hyperviscosity syndrome.[8,9] Many patients are asymptomatic at diagnosis and therapy is not indicated in these cases.[8]

Case Report

We present a case of a 50-year-old female, known to have history of ADPKD, who was referred to the internal medicine outpatient clinic after an episode of pain in the upper abdomen which led to the identification of PLD.

ADPKD had been diagnosed a decade ago and kept under regular follow-up, with normal renal function and stable renal ultrasound control. She had controlled arterial hypertension and recurrent UTI as renal manifestations. A pituitary incidentaloma was identified soon after ADPKD diagnosis, later clarified to be an asymptomatic Rathke's cleft cyst. She reported previous oral contraceptive use, no prior pregnancies and had reached menopause a year ago. Her family history was remarkable for her father who received a renal transplant in his late fifties in the setting of ADPKD without hepatic involvement and died with acute myeloid leukemia two years later.

The patient presented to the consultation with increased abdominal girth due to hepatomegaly, but without constitutional symptoms, lymphadenopathies or splenomegaly. However, considering recent normocytic anemia (hemoglobin of 10.8 g/dL; reference range (RR): 12.0 - 15.6 g/dL) and thrombocytopenia (platelet count of 129 x 10^9/L; RR: 150 - 450 x 10^9/L) during the mentioned episode and also the patient's concern about her family history, she was further evaluated. Serum protein electrophoresis revealed M band in the beta 2 region. Immunofixation showed immunoglobulin M (IgM) and kappa monoclonal protein. Serum IgM level was 14.66 g/L (RR: 0.33 - 2.93 g/L), free kappa light chain was 56.7 mg/L (RR 3.30 - 19.40 mg/L) and free kappa/lambda ratio 3.67 (RR: 0.26 - 1.65). Beta-2 microglobulin was 2.80 mg/L (RR: 0.97 - 2.64 mg/L). The bone marrow aspirate revealed the presence of 8% of kappa and IgM clonal B cells, combined with the presence of a population of 0.9% of kappa and IgM clonal plasma cells. The *L265P* mutation in *MYD88* was detected but there was no somatic mutation in *CXCR4*. Bone marrow biopsy showed infiltration by lymphoplasmacytic lymphoma cells, with a minimal population of monoclonal IgM kappa plasma cells. Immunohistochemistry was positive for CD20 and CD138. A diagnosis of Waldenström macroglobulinemia (WM) was established.

During her follow-up, her abdominal distension worsened, she had more episodes of pain in the upper abdomen and developed malnutrition.

Recently, she presented with a 3-month history of early satiety, weight loss (8 kg) and sarcopenia, and had dyspnea, orthopnea, night sweats, subfebrile temperatures and pain in the right hypochondrium for the last 2 days.

On physical examination, the patient was vigil and oriented, had a blood pressure of 94/67 mmHg, temperature of 37.5ºC, palpable exuberant hepatomegaly (5 cm below the costal margin and crossing the midline into the left hypochondrium), pain in the right hypochondrium with no rebound and was euvolemic.

Laboratory tests showed anemia of 10.7 g/dL (RR: 12.0 - 15.6 g/dL), thrombocytopenia of 127 x 10^9/L (RR: 150 - 450 x 10^9/L), leukocytosis of 11.1 x 109/L (RR: 3.90 - 10.2 x 10^9/L), C reactive protein of 24.06 mg/dL (RR: < 0.50 mg/dL) and procalcitonin of 9.59 ng/mL (RR: 0 - 0.5 ng/mL). She had hyponatremia of 125 mmol/L (RR: 135 - 145 mmol/L), low levels of magnesium (1.6 mg/dL; RR: 1.9 - 2.5 mg/dL) and albumin (3.0 g/dL; RR: 3.5 – 5.2 g/dL). Renal function, liver tests and coagulation times were normal. No evidence of proteinuria. The patient was also evaluated for her WM, that was stable and kept a slow rising IgM.

Blood cultures isolated non-extended-spectrum β-lactamase producing *Klebsiella pneumoniae*, with no resistance to tested antibiotics. Urine culture was negative.

The chest radiography showed elevation of the diaphragm and mild right pleural effusion (Fig. 1). Abdominal

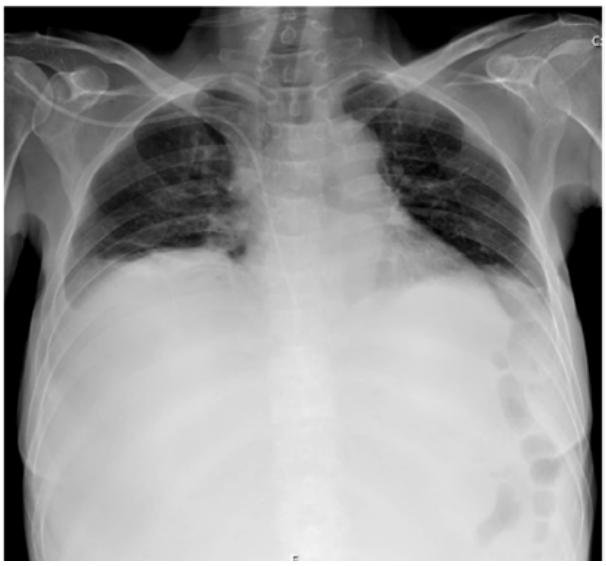

Figure 1: Chest radiography showing elevation of the diaphragm and mild right pleural effusion.

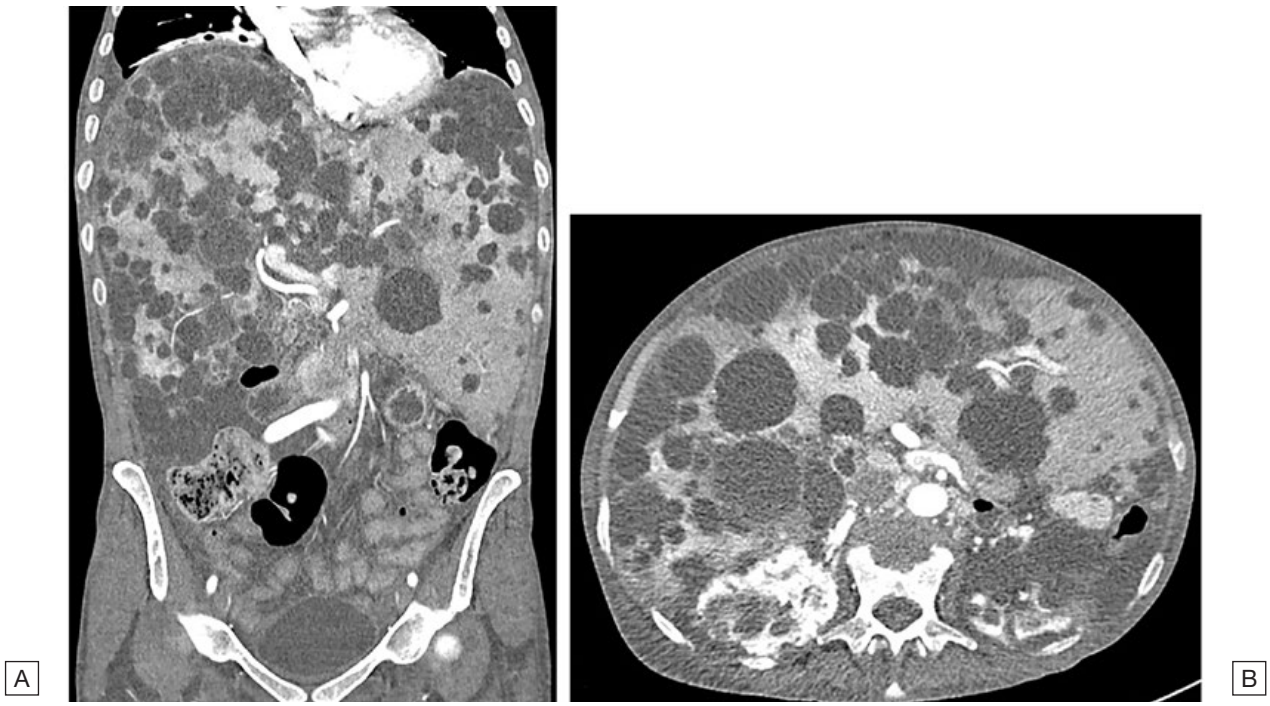

Figure 2: Abdomen and pelvis computed tomography (coronal - **A** and axial - **B** views) demonstrate massive hepatomegaly (26 cm longitudinal axis of the right lobe) with left lobe extending across the entire left flank. The liver parenchyma is diffusely replaced by countless cysts. Two cysts of the right lobe, with approximately 30 mm, have slight parietal enhancement and altered enhancement of the adjacent parenchyma (aspects suggesting infected cysts). There are numerous renal cortical cysts.

ultrasound revealed marked hepatomegaly with countless cysts, some with heterogeneous content, revealing a possible complicated nature. The kidneys had multiple cystic formations and were difficult to delimit. The abdomen and pelvis computed tomography (CT) described massive liver enlargement (26 cm longitudinal axis of the right lobe) with the left lobe extending to the entire left flank and the liver parenchyma practically replaced by countless cystic formations. Two cysts of the right lobe, both measuring approximately 30 mm, had slight parietal enhancement and altered enhancement of the adjacent parenchyma. These aspects are suggestive of infected hepatic cysts. The kidneys had dimensions at the upper limit of normal and countless cortical cysts, some of them filled with blood. No signs suggestive of infected renal cysts were identified. There was moderate volume of peritoneal effusion in the pelvis (Fig. 2).

The positron emission tomography (PET)-CT scan described countless hypodense nodular images scattered throughout the liver parenchyma and several of them exhibited peripheral 18 fluorodeoxyglucose uptake, consistent with infected cysts (Fig. 3).

The patient was started on piperacillin/tazobactam, fluids and nutritional supplementation. Within the early days, inflammatory markers, natremia and blood count nearly normalized. She completed two weeks of piperacillin/tazobactam and then switched to amoxicillin/clavulanate. After three weeks of hospitalization, she was discharged and completed a two more-week course of antibiotics. After

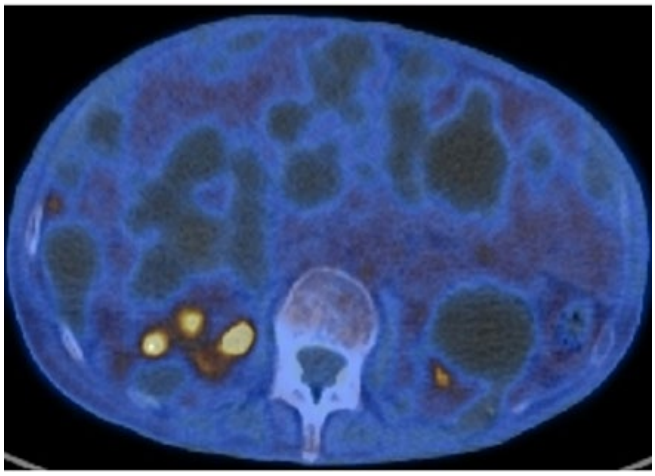

Figure 3: Positron emission tomography - computed tomography demonstrate countless hypodense nodular images scattered throughout the liver parenchyma with several of them exhibiting peripheral 18-fluorodeoxyglucose uptake (consistent with infected cysts).

2 months, the patient was proposed for liver transplant, which she refused.

Later on, she had improvement of digestive system compression symptoms and remained with normal renal function and without proteinuria. Her IgM kept on rising with a last value of 37.45 g/L. An abdomen and pelvis CT performed a year later showed a decrease in liver dimensions (18.3 cm longitudinal axis of the right lobe and 18.6 of the left lobe)

and in several hepatic cysts. There was mild volume of peritoneal effusion in the pelvis. The remaining features were similar.

Discussion

This case report illustrates several possible complications that may arise over the course of ADPKD. ADPKD is commonly caused by a germline mutation in *PKD1* or *PKD2*.[1,2,5] Clinical diagnosis is based on renal imaging.[6] In the absence of atypical findings, a genetic test is not required when there is a positive family history.[6] The number of cysts increases with age[1] and cyst enlargement that leads to capsule stretching is a cause of chronic pain.[5] Over the years, this patient remained stable under surveillance presenting with renal manifestations commonly associated with the disease, such as hypertension and UTI. Imaging occasionally described features suggestive of hemorrhagic renal cysts, one of the causes of acute pain.[5] Considering extrarenal manifestations, intracranial aneurysms are four times more prevalent in ADPKD patients than in the general population, ranging from 9% to 12%.[1,2] The risk is even higher if there is a positive family history of intracranial aneurysms, and in these patients, screening is recommended.[1,2] Despite the absence of this relation in our case, the patient was screened and a pituitary incidentaloma was found, and only later described as a Rathke's cleft cyst. This uncertainty was due to the challenging differentiation between a Rathke's cleft cyst and pituitary adenoma based on magnetic resonance imaging (MRI).[10] Although rare and not in our case, the association of ADPKD with pituitary adenoma has been described.[11]

PLD is present in more than 90% of ADPKD patients over the age of 35 years.[1] Most patients remain asymptomatic.[4,6] However, in approximately 20% of patients, symptoms arise secondary to hepatomegaly compressing adjacent organs or cyst complications.[1,4,6] In our case, this was what prompted the diagnosis. PLD diagnosis is also based on ultrasound, CT or MRI.[6,12] The severity of the disease can be classified based on the volume measured by the latter imaging methods.[6] Despite the absence of this information in our CT reports, we would empirically classify this patient as a probable severe phenotype, based on her CT image and the presence of symptoms such as pain, early satiety, decrease food intake, weight loss, sarcopenia, and dyspnea. The ascites and pleural effusion may also be present, in rare and most severe cases, secondary to hepatic venous outflow obstruction.[1,4] Although the size of cysts increase with age,[6] in this case, the female gender and previous exposure to exogenous estrogens played a major role in her disease progression and severity. Of note, this patient's last control CT showed a decrease in liver volume without treatment. This trend has been reported to happen after 48 years of age in female patients,[1] due to reduced endogenous estrogen synthesis after menopause.[12] Until then, women are recognized to have a faster progression of PLD,[6] as our case illustrates.

As with renal cysts, acute upper abdominal pain may be secondary to hepatic cyst hemorrhage, that may happen as a result of high intracystic pressure, rapid cyst growth or direct trauma.[6,12] This cyst complication may range from asymptomatic6 to unremitting pain requiring cyst fenestration or enucleation.[6,12] Some of our patient's pain episodes were attributed to hepatic cyst hemorrhage based on symptoms and CT findings. This patient eventually developed hepatic cyst infection, as described above. This is a clinical diagnosis that usually presents with pain in the right upper quadrant, fever, malaise and elevated inflammatory markers.[5,6,12] The imaging confirmation remains difficult.[13] Tough both CT and PET-CT identified features of cyst infection in our case, PET-CT is considered more sensitive.[5,6,12] Cyst fluid analysis and culture is considered the gold standard for diagnosis.[6,12] Hepatic cyst infection is believed to be the result of translocation of intestinal bacteria.[6,12] It is a serious complication due to the risk of progression to sepsis.[5,6,12] *Escherichia coli* and *Klebsiella* are the main species isolated from blood cultures or cyst aspirates,[6,12] which is consistent with our case. Treatment should be based on broad spectrum antibiotic therapy[5,12] with a minimum treatment duration of 4 weeks.[5] Cyst drainage should be considered in case of antibiotic failure.[6,12]

Liver or combined liver-kidney transplantation is the only curative therapeutic option and should be considered in cases of severe and symptomatic disease,[6] such as our patient around the described cyst infection episode.

Our patient's initial normocytic anemia could be attributable to the presence of some hemorrhagic renal and hepatic cysts. On the other hand, anemia has a reported lower prevalence in ADPKD due to endogenous elevated levels of erythropoietin,[14] even in the presence of significant CKD.[15] Cytopenia has been described in the setting of ADPKD with impaired kidney function, more consistently with lymphopenia and less with thrombocytopenia, in correlation with the stage of CKD.[14,15] Nevertheless, this patient had anemia and thrombocytopenia, which are not typical features of ADPKD. These findings warranted further evaluation of the abnormal blood tests and ultimately led to the diagnosis of WM. This diagnosis requires the presence of IgM monoclonal protein in the serum associated with the infiltration of clonal lymphoplasmacytic cells in the bone marrow.[8] As in our patient, in more than 90% of cases, the *L265P* mutation in *MYD88* is detected.[8] WM associated kidney disease is uncommon and renal manifestations are usually the result of tissue infiltration or abnormal monoclonal protein.[7] Some hematological malignancies have rarely been described[16,17] in an ADPKD patient, and our patient has a family history of such association, although secondary to immunosuppressors in the setting of renal transplantation. Though to our

knowledge, there is one described case of multiple myeloma in co occurrence with ADPKD,[17] in our search we have not found any case of ADPKD associated WM.

Considering the ADPKD background as a progressive cause of CKD and the rare but wide spectrum of nephropathies in WM, with a cumulative incidence of around 5% at 15 years,[7] a thorough and frequent monitoring should be performed in this case. ■

Contributorship Statement

IMC - Writing the manuscript, selecting the images, reviewing the literature, critically reviewing the content and approving the final version
IF - Selection of images, critical review of content and approval of final version
All authors approved the final version to be published.

Declaração de Contribuição

IMC – Redação do manuscrito, seleção das imagens, revisão bibliográfica, revisão critica do conteúdo e aprovação da versão final
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