CLINICAL IMAGE

A rare cause of galactorrhea in autosomal dominant polycystic kidney disease: pituitary stalk compression by an intracranial aneurysm

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited cause of chronic kidney disease (CKD), estimated to affect 1:500 to 1:1000 live births.[1] The disease is genetically heterogenous and arises from mutations in 1 of the 2 genes: *PKD1*, which encodes the integral membrane protein polycystin-1 (PC1), and *PKD2*, which encodes polycystin-2 (PC2) that is believed to function as a transmembrane ion channel.[1] The structure of PC1 resembles that of adhesion receptors;[2] the protein is thought to act as an atypical G-protein in transmitting chemo- and mechanosensory data form the adjacent cilia and external environment.[2] In addition to its role in calcium-dependent signaling pathways, PC2 appears to facilitate PC1 maturation and localization.[2] PC1 and PC2 associate to form a receptor-channel complex that modulates fluid transport, cell differentiation and proliferation, and adhesion.[2]

Both PC1 and PC2 are expressed in the tubular epithelium.[1] Disordered cell maturation and aberrations in fluid translocation underly the development of renal cysts, which are the hallmark of ADPKD. The expansion of these cysts over time results in a loss of normal renal parenchyma and, eventually, kidney failure (KF). The expression of PC1 and PC2 in other organ systems, such as the liver, heart, bone, and muscle tissues,[1] explains the multiorgan nature of the disorder. Both PC1 and PC2 are present in endothelial and vascular smooth muscle cells.[3] Evidence suggests that PC1 plays an important role in maintaining the structural integrity of the vasculature; the loss of its expression may mediate the association of ADPKD with intracranial aneurysm (ICA) formation.[3]

A considerable variability exists in the clinical severity and extrarenal manifestations of ADPKD. Intrafamilial phenotypic variation suggests that an additional somatic mutation in the remaining wild-type gene contributes to the disease severity.[4] Antecedent first-degree family history of ICA increases the risk of its development in an individual patient, which suggests that the type of germline mutation may be an important determinant in ICA formation.[3] A history of smoking, presence of hypertension, and CKD stage may increase the ICA risk in patients with ADPKD.[5]

ICA occurs in 5% to 9% of patients with ADPKD, and its prevalence is 3 to 5 times greater than in the general population.[3] The anterior circulation of the circle of Willis is the most common site of ICA formation.[3,5] Most ICAs are small in size and are commonly diagnosed on screening;[5] local pressure effects are commensurably rare. Here, we report a patient with known KF due to ADPKD, who developed symptomatic hyperprolactinemia caused by pituitary stalk compression by an ICA of the internal carotid artery.

A 25-year-old man of Black African ethnicity presented to a district-level hospital in 2018 with elevated blood pressure and fluid overload. Biochemical workup confirmed KF with an estimated glomerular filtration rate of 6 ml/min/1.73 m^2 at index presentation, and the patient was transferred to our center for evaluation. Abdominal ultrasound on admission showed large kidneys with multiple cysts bilaterally, leading to a diagnosis of ADPKD. In the absence of genetic testing in a resource-limited environment, APDKD was considered to be due to *PKD1*-related disease in view of an early presentation with established KF. A family history of the disorder was not known to the patient. Following stabilization of uremia with emergent hemodialysis, the patient was transitioned to continuous ambulatory peritoneal dialysis, and subsequently wait-listed for a deceased-donor kidney transplantation.

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Received: October 31, 2022.
Revision accepted: November 2, 2022.
Published online: December 5, 2022.
Pol Arch Intern Med. 2022; 132 (12): 16367
doi:10.20452/pamw.16367

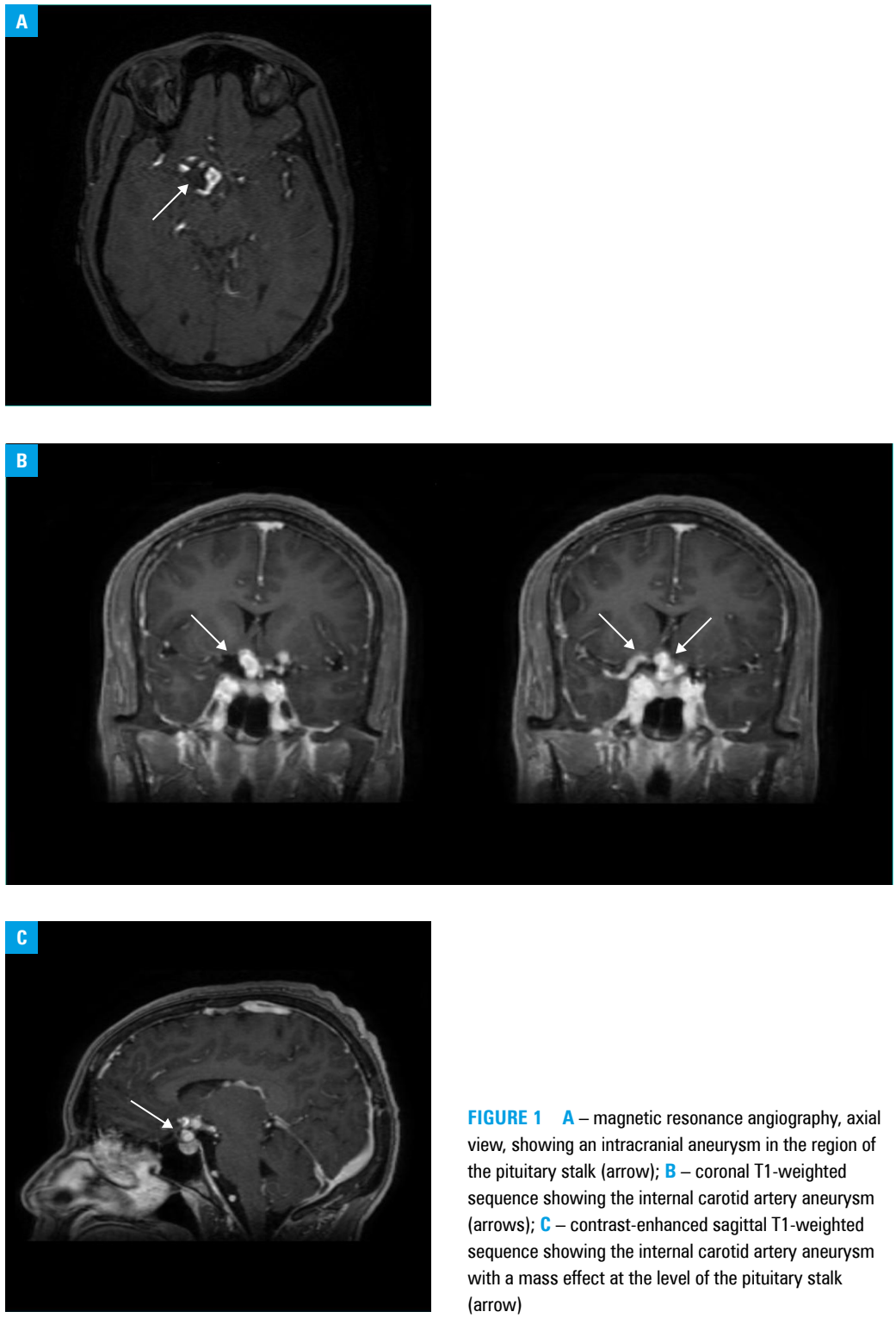

FIGURE 1 **A** – magnetic resonance angiography, axial view, showing an intracranial aneurysm in the region of the pituitary stalk (arrow); **B** – coronal T1-weighted sequence showing the internal carotid artery aneurysm (arrows); **C** – contrast-enhanced sagittal T1-weighted sequence showing the internal carotid artery aneurysm with a mass effect at the level of the pituitary stalk (arrow)

During a routine follow-up in March 2021, the patient reported swollen and tender breasts. Clinical examination revealed bilateral gynecomastia with galactorrhea. Neurological examination was unremarkable. Biochemistry confirmed an elevated prolactin level of 26.7 μg/l (reference range [RR], 3.0–11.6 μg/l). Adrenocorticotropic hormone levels were decreased at 0.9 pmol/l (RR, 1.6–13.9 pmol/l), with a normal cortisol level of 306 nmol/l (RR, 133–537 nmol/l). Other pituitary hormone levels were within the reference ranges, with normal luteinizing hormone, follicular stimulating hormone, thyroid stimulating hormone and insulin-like growth factor 1 levels documented.

Non–contrast-enhaced magnetic resonance angiography (MRA) of the brain yielded an image of 2 ICAs—a fusiform right distal internal carotid artery aneurysm measuring 6.5 mm in length and 9.9 mm at the maximal diameter, and a saccular left middle cerebral artery aneurysm measuring 1.7 mm at the neck and 4.5 × 5.2 mm at the dome (FIGURE 1A and 1B). A local mass effect around the internal carotid artery aneurysm with compression of the pituitary stalk was noted (FIGURE 1C). This finding accounted for

hyperprolactinemia and the resultant galactorrhea in the present case; the pituitary gland itself being radiologically normal.

The patient was referred to the neurosurgery department for consideration of endovascular coil embolization. In the absence of known risks for ICA rupture, conservative management with medical treatment of galactorrhea and serial MRAs to monitor for ICA enlargement were recommended. At present, the patient remains stable on peritoneal dialysis, and reports improvement in galactorrhea.

ICAs occur more frequently in patients with ADPKD than in the general population, although their actual prevalence in ADPKD is relatively low (5%–9%).[3,4] The rate of growth of ICA in ADPKD patients developing the complication is similar to that observed in the general population.[3] ICA rupture leading to subarachnoid hemorrhage is the most serious complication. Longitudinal studies of patients with ICA detected on radiological screening suggest a relatively low risk of rupture.[5] Patients with posterior circulation ICA, ICA greater than 10 mm, and those with a personal or family history of subarachnoid hemorrhage are at an increased risk of rupture.[4]

Neurological deficit arising from local pressure symptoms caused by ICA enlargement may include seizures, transient ischemic attacks, and cranial nerve palsies (especially of the oculomotor nerve); however, such presentations are rare in ADPKD,[4,6] possibly reflecting the small size of ICA in the affected patients.[5]

Prolactin secretion by the pituitary is tonically inhibited by dopamine released from the hypothalamus into the portal venous system. Compression of the pituitary stalk inhibits the flow of dopamine and releases this inhibition, potentially resulting in hyperprolactinemia. ICAs are a rare but known cause of hyperprolactinemia due to pituitary stalk compression—such cases are often accompanied by a loss of other pituitary hormones secretion. Less than 2% of all ICAs are located in the region of the sellar within sufficient proximity to cause stalk compression.[6] As a result, ICAs contribute to less than 0.17% of such cases;[6] only 35 cases have been described in the literature to date.[6] Aneurysms of the internal carotid artery are most commonly implicated in the cases of ICA-related stalk compression.[6] Although the internal carotid artery is the most common site of ICA formation in ADPKD,[5] the present case is, to our knowledge, the first report of pituitary stalk compression in the context of an APDKD-related ICA.

Recovery of the normal pituitary function after ICA occlusion is uncommon.[6] In the absence of risks for rupture as defined above, symptomatic relief may be obtained through the use of dopamine agonists, such as bromocriptine or cabergoline. In the present case, such an intervention resulted in a significant improvement in gynecomastia and galactorrhea.

Current guidelines restrict screening for ICA to the patients identified as being at high risk of rupture due to a family history of intracranial bleeding.[4] Although ICA rupture carries a significant risk for mortality, substantial morbidity may occur as a result of local pressure effects caused by aneurysm growth. Clinicians should therefore maintain a high index of suspicion for unusual presentations, such as galactorrhea and other manifestations of pituitary dysfunction, which in the context of ADPKD should carry a low threshold to screen for ICA formation.

ARTICLE INFORMATION

NOTE This paper won the 3rd award at the 2022 Best Case Report Contest; MIRCIM, October 1, 2022.

ACKNOWLEDGMENTS None.

FUNDING None.

CONFLICT OF INTEREST None declared.

HOW TO CITE Blomerus E, Dayal C, Davies M. A rare cause of galactorrhea in autosomal dominant polycystic kidney disease: pituitary stalk compression by an intracranial aneurysm. Pol Arch Intern Med. 2022; 132: 16367. doi:10.20452/pamw.16367

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