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PIK3CA-Related Overgrowth Syndrome: A Case Report

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Abstract: *PIK3CA*-related overgrowth syndrome (PROS) is characterized by a range of mutations in the phosphoinositide 3-kinase (PI3K) pathway, resulting in diverse and variable imaging findings. Hyperplasia in PROS can affect multiple organ systems and commonly presents with asymmetric limb and brain enlargement, venous anomalies, and pigmented nevi. While genetic testing for PROS may be considered in the presence of these features, diagnosis and treatment are often delayed in patients with atypical phenotypes or those without visible external anomalies. We report a case of newly diagnosed PROS in a 20-year-old woman with a lifelong history of abdominal pain. This patient exhibited no external signs of the disease and had unusual vascular manifestations identified through imaging. The unique clinical and imaging features in this case provide valuable insight into the broad spectrum of PROS findings and offer guidance for radiologists in recognizing these elements.

Keywords: *abdominal imaging, PIK3CA-Related Overgrowth Syndrome, PROS, hyperplasia*

Introduction

PIK3CA-related overgrowth syndrome (PROS) is a rare disorder caused by hyperactivation mutations in the *PIK3CA* gene that lead to abnormal cell growth and development. Recent advances in genetic sequencing have allowed for the unification of many conditions that were previously believed to be distinct; however, the full spectrum of clinical manifestations of PROS remains unknown. The case presented here involves a young woman with lifelong abdominal pain, who was eventually found to have vascular malformations and genetically confirmed PROS. This case report was prepared following the CARE guidelines[1] and highlights the need for increased awareness among radiologists of PROS and its diverse features.

Key Points

- Atypical PROS presentations, often lacking overt external stigmata but manifesting with complex internal vascular and growth dysregulation, demand a high index of suspicion from advanced imaging studies for early recognition.
- Multimodality imaging, including MRI, CT, US, and CTA or MRA, is critical for precisely characterizing the diverse and subtle visceral and cerebral anomalies in PROS, which can prompt definitive molecular testing.
- Recognizing the broad imaging spectrum of PROS facilitates timely genetic confirmation of *PIK3CA* mutations, which is increasingly relevant for guiding the implementation of targeted pharmacologic interventions.

Case Presentation

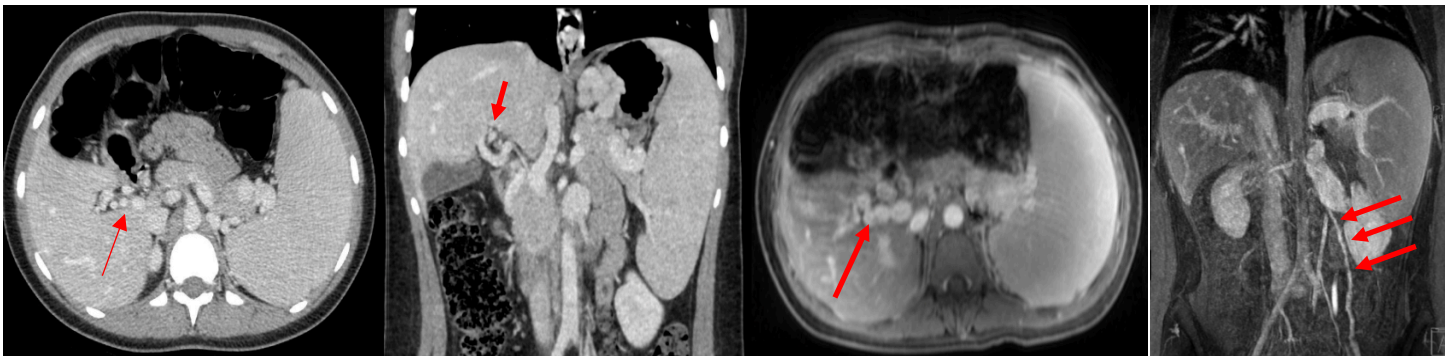
A 14-year-old girl with a history of immune thrombocytopenic purpura presented to the emergency department at an outside hospital for an asthma exacerbation. Chest radiograph findings demonstrated low lung volumes, increased peribronchial thickening, and a dilated, air-filled stomach. A computed tomography (CT) scan of the chest incidentally identified esophageal

Abbreviations
AVM: arteriovenous malformation
CLOVES: congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal syndrome
CT: computed tomography
CTA: computed tomography angiography
EGD: esophagogastroduodenoscopy
FAO: fibroadipose hyperplasia or overgrowth
FAVA: fibroadipose vascular anomaly
HHML: hemihyperplasia multiple lipomatosis
IMV: inferior mesenteric vein
KTS: Klippel-Trenaunay syndrome
MCAP: megalencephaly-capillary malformation syndrome
MRA: magnetic resonance angiography
MRI: magnetic resonance imaging
PARTO: plug-assisted retrograde transvenous obliteration
PROS: *PIK3CA*-related overgrowth syndrome

varices. This prompted a CT scan of her abdomen (Figure 1), which revealed cavernous transformation of the portal vein and splenomegaly, along with esophageal, gastric fundal, and perisplenic varices. The CT scan also revealed right-sided hydronephrosis, which was attributed to a retrocaval ureter. The liver contour appeared normal. At that time, an outside provider initiated a diagnostic workup, including a liver biopsy, to determine the underlying cause of the patient's portal hypertension. However, the evaluation was inconclusive. Given the absence of significant symptoms and identifiable etiology, the patient was followed closely by pediatric gastroenterology. In the period following the patient's initial diagnosis of portal hypertension, she experienced multiple episodes of gastroesophageal variceal bleeding. She experienced repeated bleeding episodes despite treatment attempts to manage them endoscopically with sclerotherapy and variceal band ligation. At age 15, the patient presented with massive variceal bleeding and underwent emergent plug-assisted retrograde transvenous obliteration (PARTO), followed by the creation of a low-flow modified mesocaval shunt utilizing the inferior mesenteric vein-to-left renal vein. Following the placement of the shunt, the patient remained clinically stable with no further episodes of gastrointestinal bleeding and continued to be monitored routinely.

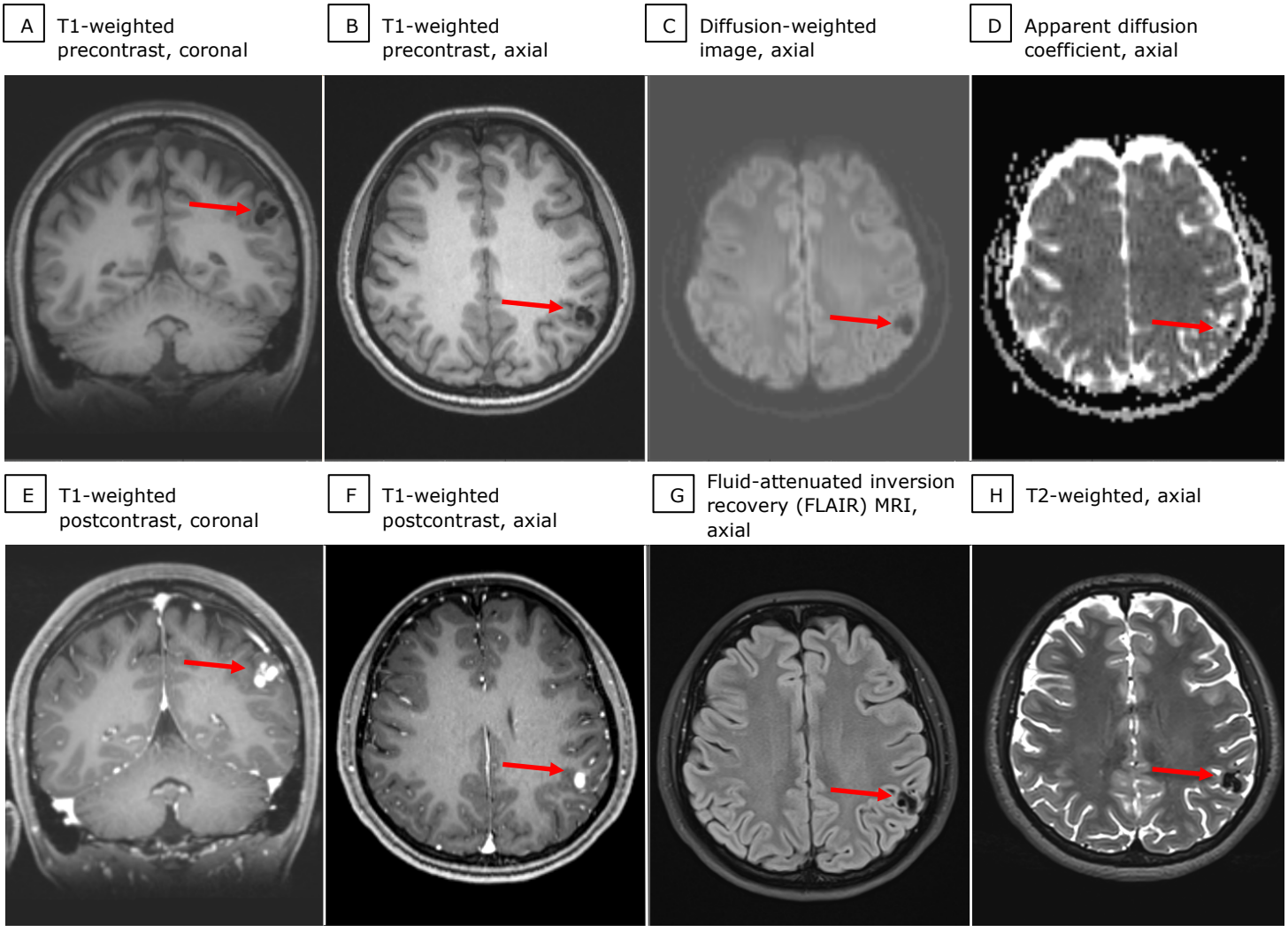
At age 18, the patient developed new numbness and weakness in her right arm and leg. Brain magnetic resonance imaging (MRI), followed by cerebral angiography (Figure 2), revealed a left

Figure 1. Cavernous Transformation of the Portal Vein with Associated Portal Hypertension Before and After PARTO and IMV-Left Renal Vein Shunt



(A) Axial and (B) coronal contrast-enhanced computed tomography images illustrate cavernous transformation of the portal vein (arrows). Also visualized are splenomegaly, esophageal and gastric fundal varices, and normal liver morphology. (C) An axial magnetic resonance venogram following PARTO and IMV-left renal vein shunt also shows cavernous transformation of the portal vein (arrow). (D) A coronal maximal intensity projection (MIP) magnetic resonance venogram (MRV) shows the course of the redirected IMV (arrows) onto the left renal vein, which allowed for mesocaval shunting.

Figure 2. Brain MRI of 18-Year-Old Woman with PROS and Arteriovenous Malformation



Magnetic resonance images of the patient's brain illustrate a Spetzler-Martin grade 1 AVM (red arrows), for which this patient subsequently underwent a left parietal craniectomy.

parietal arteriovenous malformation (AVM) of Spetzler-Martin grade 1. Given her neurological symptoms, the AVM was surgically resected. Her postoperative recovery was complicated by focal seizures, but these were controlled with antiepileptic medication.

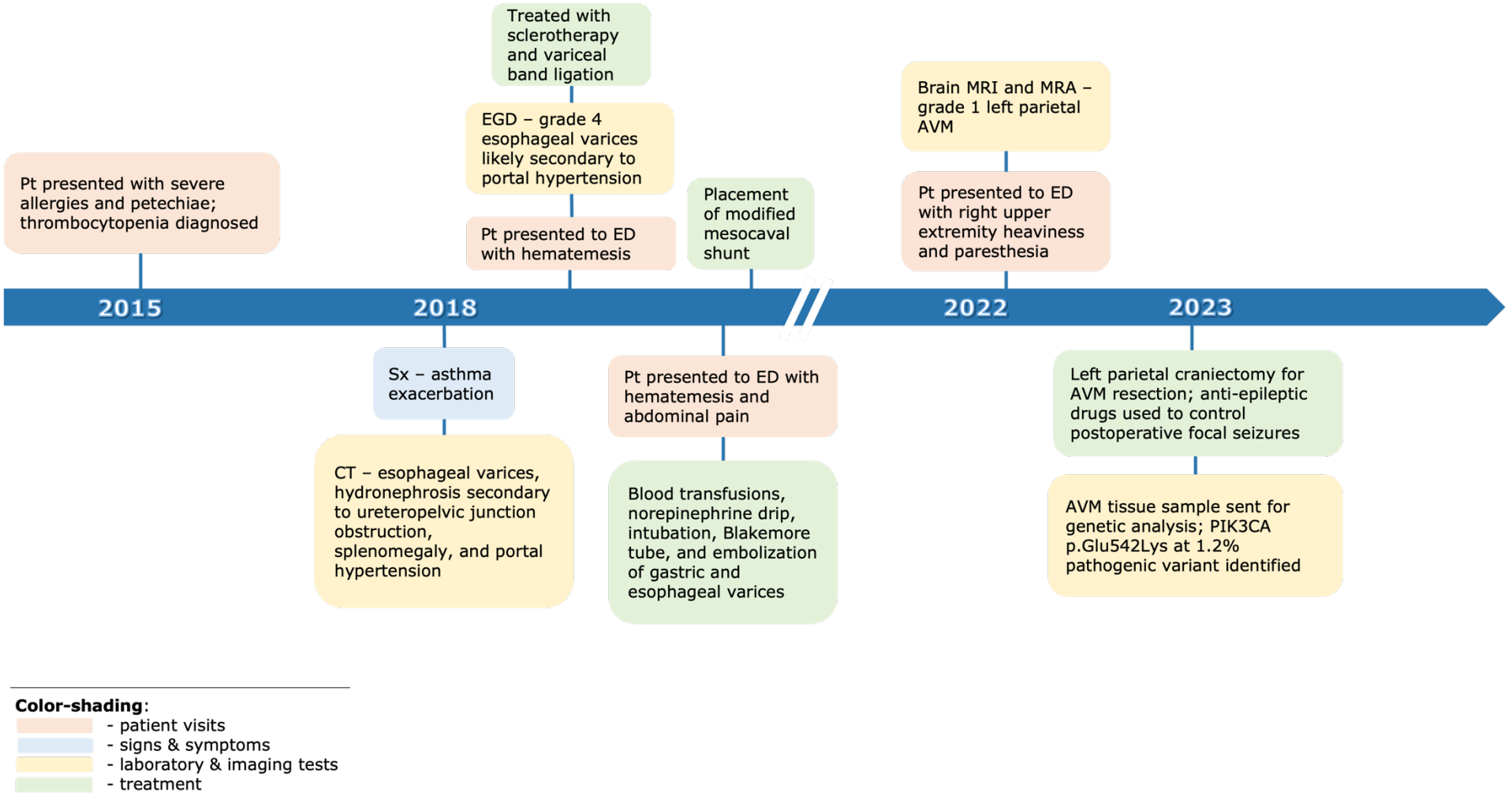
Considering the patient's history of multiple vascular anomalies, blood, skin punch biopsy, and AVM tissue were submitted to Children's Hospital Los Angeles for genetic evaluation with a VMD4Kids (Vascular and Mosaic Diseases for Kids) panel. Genetic analysis of the resected AVM tissue identified a pathogenic *PIK3CA* p.Glu542Lys variant present at 1.2%, consistent with PROS. Additional genetic testing detected variants of uncertain significance in *CTNNB1* c.1697T>C and p.Met566Thr.

This patient is currently undergoing baseline brain and abdominal MR imaging in preparation for initiation of alpelisib therapy.

Discussion

PIK3CA-related overgrowth syndrome encompasses a range of congenital disorders caused by somatic, activating mutations in the PI3K/AKT/mTOR pathway.[2] The PROS phenotype, which varies depending on mutation timing and mosaicism, is characterized by asymmetric,

Case report timeline.



Abbreviations: AVM, arteriovenous malformation; CT, computed tomography; ED, emergency department; EGD, esophagogastroduodenoscopy; MRI, magnetic resonance imaging; Pt, patient; Sx, symptoms

segmental overgrowth of vessels, soft tissues, and bone. Due to its genetic and phenotypic diversity, PROS is challenging to identify and manage, especially in cases without obvious malformations. Advances in gene sequencing have linked several previously separate phenotypes to *PIK3CA* mutations, now recognized under the PROS spectrum.[2]

PROS conditions are characterized by overgrowth, often lipomatous, primarily in the limbs (including digits), trunk, face, and brain. Brain overgrowth may also involve ventriculomegaly, corpus callosum enlargement, and cerebellar tonsillar ectopia. Hyperplasia may cause lymphatic anomalies and vascular malformations, including capillary, venous, and, less commonly, arterial and mixed forms. Of note, cutaneous features like pigmented nevi and renal manifestations such as hydronephrosis secondary to the position of the ureter, as seen in this case, and cysts are also common.[3] Diagnosis is made by molecular identification of a somatic *PIK3CA* mutation that is sporadic and onsets early in childhood. Presentation may be syndromic with pleomorphic involvement or localized with isolated features like macrodactyly, truncal adipose overgrowth, or large lymphatic malformation.[2] Symptoms depend on the affected organ and the extent ofovergrowth.

PROS conditions most associated with vascular malformations include congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal syndrome (CLOVES), Klippel-Trenaunay syndrome (KTS), fibroadipose vascular anomaly (FAVA), and megalencephaly-capillary malformation syndrome (MCAP), all of which express well-defined clinical and imaging findings.[4] CLOVES features lipomatous trunk overgrowth, lymphatic and slow-flow capillary (port-wine stain) and venous malformations, epidermal nevi, and spinal deformities like scoliosis.[5] KTS presents with a classic triad of port-wine capillary malformations, low-flow vascular malformations, and hypertrophy of a single lower extremity.[6] FAVA involves phlebectasia, a painful, enlarging calf mass, and contractures.[5] MCAP is characterized by focal overgrowth, cutaneous capillary malformations, megalencephaly, syndactyly, and polydactyly.[3]

While deep vein thromboembolism and pulmonary embolism are well-documented in PROS patients, vascular findings from this case like chronic portal vein occlusion and cavernous transformation of the portal vein are rarely reported. More typical vascular anomalies in people with PROS affect peripheral areas, overlying the affected limbs, trunk, or face.[7] Finally, while this patient has multiple AVMs, including a cerebral AVM, PROS vascular deformities are mostly capillary, venous, and lymphatic.[7]

While molecular testing is essential to confirm PROS, radiologists familiar with the clinical and radiologic findings associated with PROS can help identify this rare disease in pediatric patients. In our case, MRI of the central nervous system and abdomen was instrumental in characterizing multiple vascular malformations and unilateral hydronephrosis through enhanced soft tissue contrast, revealing a syndromic presentation. Key imaging features suggestive of PROS include asymmetric fat hypertrophy, slow-flow venous or lymphatic malformations, infiltration into surrounding tissue, cortical malformations, and

Table. Characteristic Imaging Features of PROS by Affected Area[3,5]

Affected Area and Imaging Modality	Imaging Features
Brain MRI (without contrast)	• Hemimegalencephaly • Ventriculomegaly and hydrocephalus • Cerebellar tonsillar ectopia • Cortical malformations
Spinal cord ultrasound (for neonates) or spinal MRI	• Tethered cord • Lipomyelomeningocele • Vertebral anomalies
Whole body MRI	• Trunk overgrowth • Lymphatic malformations • Vascular malformations
Limb radiography and MRI	• Limb overgrowth • Lymphatic malformations • Vascular malformations • Thromboembolism
Renal ultrasound and Doppler ultrasound	• Enlarged kidneys • Tumors • Cysts • Renal malformations

sclerotic bone changes.[2] Current imaging recommendations for PROS are based on the affected organ (Table).[2,3]

Other conditions that can appear similarly to PROS include Proteus syndrome, a syndrome caused by an *AKT1* mutation that is rarely congenital; *PTEN* hamartoma tumor syndrome; tuberous sclerosis; and neurofibromatosis I.[7] PROS testing should be considered in patients with syndromic presentations like congenital musculoskeletal overgrowth, vascular malformations, epidermal nevi, patterning defects, and central nervous system malformations.[2] Diagnosis is confirmed with a dermal biopsy or surgical excision of affected tissues.[7] The separate radiologic findings (eg, vascular malformations and the enlargement of muscle or subcutaneous fat) should prompt radiologists to consider a congenital cause like PROS. Future efforts should focus on developing a standardized protocol for follow-up imaging in PROS patients.

Currently, there are no validated standards of care for patients with PROS. However, a recent study in patients with CLOVES demonstrated clinical improvement in participants treated with the phosphoinositide 3-kinase (PI3K) inhibitor alpelisib (BYL719), ultimately leading to the drug's FDA approval.[8]

Conclusion

This case underscores the importance of considering *PIK3CA*-related overgrowth syndrome in patients without obvious external features and with less typical clinical findings. PROS testing is often reserved for patients with more apparent signs, such as unilateral limb enlargement, overlying venous anomalies, and nevi, which can delay diagnosis in ambiguous presentations such as this one. Given the multisystem involvement in PROS, radiologists can identify potential cases by connecting seemingly separate findings on imaging. Additionally, this case highlights the need for increased awareness of PROS, particularly its less common presentations, to ensure timely diagnosis. In this case, an earlier diagnosis could potentially have mitigated the degree of vascular structural changes, especially esophageal and gastric variceal development, and bleeding the patient experienced. Recognition of PROS as early as possible in a patient's clinical course enables proactive treatment strategies to be made.

Author Contributions

Conceptualization M.K.P., J.E.C., K.M.K.; Acquisition and interpretation M.K.P., J.E.C., K.M.K.; Writing - original draft preparation, K.M.K.; Reviewing and editing M.K.P., J.E.C., K.M.K.; Supervision M.K.P., J.E.C.

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