Temporal Evolution and Management of Fast Flow Vascular Anomalies in PTEN Hamartoma Tumor Syndrome

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Abstract

Phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome (PHTS) is characterized by formation of recurrent benign tumors described as PTEN hamartoma of soft tissue that may contain fast flow vascular anomalies (FFVA). The purpose of this study is to review the temporal evolution and management of FFVA in PHTS. A retrospective review of 22 patients (9 males), age 1 to 18 (median 9) years diagnosed with PHTS at a tertiary care pediatric hospital between October 2002 and August 2017 revealed 4 patients with FFVA. Imaging, management, and treatment complications were reviewed. During median follow-up of 8 (range: 4–13) years, ultrasound and magnetic resonance imaging performed for recurrent pain, showed progressive increase in the size of hamartomas and development of new FFVA in three-fourth patients. Medical management included pain medications, oral sirolimus, and physical and psychiatric therapy. Surgical excision of hamartoma ($n = 1$) resulted in recurrence within 3 months. Between 4 and 24 (average 1.5/year) embolizations were performed per patient. Pain related to FFVA responded well to embolization. Pain secondary to PTEN hamartoma responded poorly to percutaneous sclerosant injection, but demonstrated improvement with sirolimus. There was no correlation between serum sirolimus levels and frequency/timing of recurrence of FFVA/hamartoma. Complications included sclerosant migration into digital arteries ($n = 1$), subclavian vein stenosis due to glue migration ($n = 1$), oral mucositis ($n = 4$), and elevated triglycerides ($n = 4$). Patients with PHTS present with recurrent pain requiring life-long management with a multi-disciplinary team. Pain due to FFVA responds to embolization, and pain due to hamartoma responds to sirolimus. This improves quality of life, but does not prevent disease progression.

Keywords

- PTEN Hamartoma Tumor Syndrome
- PTEN hamartoma of soft tissue
- vascular anomaly
- arteriovenous malformation
- sirolimus
- embolization
- sclerotherapy

Phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome (PHTS) includes a heterogeneous group of allelic disorders, such as Bannayan–Riley–Ruvalcaba syndrome, Cowden syndrome, Proteus syndrome, and Proteus-like syndrome that share a germline mutation of the PTEN gene.^{1–3}

Patients that are suspected to have PHTS based on the National Cancer Institute revised clinical diagnostic criteria (► **Table 1**) are subjected to genetic testing for confirmation of PHTS.^{4,5} One of the features of PHTS is development of recurrent diffuse infiltrative intramuscular tumors called

Table 1 National Cancer Institute Revised Clinical Diagnostic Criteria for PTEN hamartoma tumor syndrome⁴

Major criteria
Breast cancer Epithelial endometrial cancer Follicular thyroid cancer Gastrointestinal hamartomas ≥ 3 (including ganglioneuromas, but excluding hyperplastic polyps) Lhermitte–Duclos disease (adult) Macrocephaly (adult female >58 cm, adult male >60 cm, and children $\geq 97\%$ head circumference ⁵) Macular pigmentation of the glans penis Multiple (≥ 3 of each) mucocutaneous lesions: trichilemmomas, acral keratosis, neuromas, and oral papillomas
Minor criteria
Autism spectrum disorder Colon cancer ≥ 3 Esophageal glycogenic acanthosis ≥ 3 Lipomas Intellectual disability Renal cell carcinoma Testicular lipomatosis Papillary thyroid cancer Thyroid structural lesions (e.g., adenoma and multinodular goiter) Vascular anomalies (including multiple intracranial developmental venous anomalies)
Operational diagnosis in an individual (either of the following)
(1) Three or more major criteria, but one must include macrocephaly, Lhermitte–Duclos disease, or gastrointestinal hamartomas; or (2) Two major and three minor criteria.
Operational diagnosis in a family where one individual meets revised PHTS clinical diagnostic criteria or has a PTEN mutation
(1) Any two major criteria with or without minor criteria; or (2) One major and two minor criteria; or (3) Three minor criteria.

Abbreviation: PHTS, PTEN hamartoma tumor syndrome; PTEN, phosphatase and tensin homolog.

PTEN hamartoma of soft tissue (PHOST) that may contain fast flow vascular anomalies (FFVA).^{6–8} Patients with PHTS need life-long support and management for recurrent symptoms and cancer screening.³ The use of oral sirolimus,⁹ surgical excision of PHOST,¹⁰ and embolization of FFVA^{11,12} have been reported, but a comprehensive management approach with the role of each treatment modality has not been outlined. The purpose of this study is to report the temporal evolution and management of FFVA in patients with PHTS using a multidisciplinary approach.

Materials and Methods

An institutional review board approved, retrospective review of 22 patients (M:F = 9:13) in the age range of 1 to 18 (median 9) years diagnosed with PHTS (on the basis of heterozygous germline mutation) at a tertiary care pediatric hospital between October 2002 and August 2017 was performed, and 4 patients with FFVA were identified. Patient demographic information, clinical features of PHTS, and location of PHOST are outlined in ►Table 2. Imaging studies

Table 2 Patient demographics and clinical features of PTEN hamartoma tumor syndrome

Patient	Age at first presentation (years)	Gender	Clinical features of PTEN hamartoma tumor syndrome	Follow-up (years)	Location of PTEN hamartoma and fast flow vascular anomaly
1	4	M	Macrocephaly, penile freckling, and thyroid nodules	13	Right foot and calf (at presentation), left neck and chest (at age 11 years)
2	8	F	Macrocephaly, rectal polyps, and thyroid nodules	7	Right foot and calf
3	4	M	Macrocephaly, penile freckling, thyroid nodules, and dermatofibroma	10	Left hand and forearm
4	10	M	Macrocephaly, penile freckling, and thyroid nodules	4	Right foot and ankle

Abbreviation: PTEN, phosphatase and tensin homolog.

(ultrasound, magnetic resonance imaging [MRI], angiography), management (medical, surgical, and interventional radiology [IR]), and treatment complications were reviewed. Sirolimus dose, serum sirolimus levels, response to pain, compliance with treatment, and complications were reviewed. The number of IR embolization procedures, approach, agents, and complications were reviewed.

Results

Four out of 22 (3 males) patients with PHTS demonstrated FFVA within the PTEN hamartoma. All patients initially presented with pain and swelling related to the FFVA. During clinical evaluation, all patients had macrocephaly (►Table 2). Additionally all three males had penile lentigines/freckling. The association of macrocephaly, vascular anomalies, and macular pigmentation of the glans penis constituted two major and one minor criteria for PHTS.^{4,5} The female patient

had macrocephaly, vascular anomalies, and mild intellectual disability (one major and two minor criteria). Based on these clinical criteria, genetic testing was performed, and the diagnosis of PHTS was confirmed.

In three patients, the PTEN hamartoma and FFVA involved more than one anatomical body part, but were contiguous (►Fig. 1). One patient (patient 1) developed a new non-contiguous (left chest wall) hamartoma and FFVA 7 years after the diagnosis of the initial lesion (right foot and calf). During follow-up, ultrasound and MRI performed for evaluation of recurrent pain demonstrated progressive increase in the size of the PTEN hamartoma (►Fig. 2a) and development of new FFVA within existing hamartoma in three-fourth patients (►Fig. 2b). In addition to previously described angiographic features such as arteriovenous, arteriovenous, and arteriovenous anomalies, segmental-beaded arterial ectasia of the proximal peroneal artery and side-to-side fistula with the adjacent peroneal vein was seen in

Fig. 1 A 4-year-old boy presented with right foot pain and swelling. Investigation revealed PTEN hamartoma tumor syndrome. (a) Sagittal T2-weighted foot MRI, coronal T2- (b) and (c) coronal T1-weighted calf MRI show infiltrative intramuscular soft tissue tumor in the plantar soft tissues of the foot (white arrows) and posterior compartment of the calf (black asterisk) with ectopic fat suggestive of PTEN hamartoma of soft tissue. (d) Right popliteal angiogram at presentation shows arteriovenous anomaly in the hind foot (black arrow), supplied by branches of distal posterior tibial artery, and (e) arteriovenous fast flow anomaly in the calf (black arrow), supplied by branches of proximal posterior tibial artery. MRI, magnetic resonance imaging; PTEN, phosphatase and tensin homolog.

Fig. 2 Temporal evolution of PTEN hamartoma and fast flow vascular anomaly. (a) Sagittal T2-weighted foot MRI at 5-year follow-up shows enlargement of hamartoma (black asterisk) and extension into subcutaneous tissues. (b) Coronal T2-weighted calf MRI at 9-year follow-up shows signal voids within the hamartoma (black arrow) suggestive of new fast flow vascular anomaly. (c) Right popliteal angiogram at 10-year follow-up shows segmental-beaded arterial ectasia of the proximal peroneal artery (solid black arrow) and direct side-to-side fistula with the peroneal vein (dashed black arrow). (d) Frontal digital subtraction post embolization popliteal angiogram and (e) fluoroscopic image of the calf show occlusion of arteriovenous fistula using percutaneous transvenous occlusion of the peroneal vein with coils and Amplatzer plugs. MRI, magnetic resonance imaging; PTEN phosphatase and tensin homolog.

patient 1 (→Fig. 2c). This was managed with percutaneous transvenous embolization of the peroneal vein (→Fig. 2d and e).

Medical Management

Medical management included oral sirolimus (mammalian target of rapamycin [mTOR] inhibitor) that was recommended to all four patients. The medication was started at a dose of 0.8 mg/m²/dose twice daily 3 months to 6 years after the initial presentation. Serum levels of sirolimus were monitored, and dose was titrated to target trough levels of 7 to 10 ng/ml. There were periods when families decided to hold the medication due to various reasons, but all patients had been on/off sirolimus during the study (→Fig. 3). During sirolimus therapy, patients were advised to respect a low-fat diet, and basic hematologic and metabolic screening (complete blood count, electrolytes, renal and hepatic function tests, and serum triglyceride levels) were monitored monthly. In addition, live vaccines were contraindicated, and *Pneumocystis jiroveci pneumonia* prophylaxis was administered. Patients underwent regular clinical follow-up to

monitor response to treatment. Pain secondary to hamartoma responded to sirolimus, but recurred upon the discontinuation of the medication. There was no correlation between serum sirolimus levels and frequency or timing of recurrence of hamartoma or FFVA (→Fig. 3). Complications related to sirolimus were as follows: (1) oral mucositis in all patients managed with local treatment, (2) elevated triglycerides managed with low-fat diet and improved control of serum sirolimus level, and (3) noncompliance with daily dosing resulting in variable serum levels (→Fig. 3).

All patients were enrolled in a regular physical therapy program that focused on strengthening and range of motion of the involved muscles particularly during the recovery period after IR procedures.

Surgical Management

Surgical excision was performed in one patient (patient 3) with PTEN hamartoma in the hand and forearm. This was helpful in short-term improvement in range of motion of the hand, but was followed by recurrent symptomatic hamartoma and FFVA in 3 months.

Fig. 3 Graphical representation of serum sirolimus levels and correlation with frequency and timing of interventional procedures. PTEN phosphatase and tensin homolog.

Interventional Radiology Management

The following two types of IR treatments were performed based on imaging findings and the character of the patient's pain: (1) staged embolization of FFVA using transarterial, percutaneous intranidal, percutaneous, and retrograde transvenous approaches and (2) percutaneous interstitial sclerosant injection of PTEN hamartoma. Patients presenting with pain at and/or distal to the location of FFVA that was worse with activity and relieved with rest were managed with staged embolization of FFVA since this type of pain was typical of steal phenomenon due to arteriovenous shunting. Patients with constant pain unrelated to activity at the site of PTEN hamartoma that occurred despite complete/near complete embolization of FFVA were thought to have pain due to

tumor proliferation and hypertrophic nerves and were managed with intratumoral injection of sclerosant.

A variety of embolic and sclerosing agents such as Dehydrated Alcohol (Akorn, Lake forest, IL), Bleomycin (APP Pharmaceuticals, Schaumburg, IL), 3% Sodium tetradecyl sulfate (Sotradecol®, Mylan®, Canonsburg, PA), Trufill® n-butyl-2-cyanoacrylate (n-BCA; Codman, Raynham, MA), Histoacryl® (B. Braun Surgical, S.A., Rubi, Spain), Onyx® liquid embolic system (Medtronic, Minneapolis, MN), Concerto™ and Axiom™ detachable coils (Medtronic, Minneapolis, MN), and Amplatzer™ Vascular Plugs (St. Jude Medical Inc., St. Paul, MN) were utilized. Besides initial staged management of FFVA, repeated IR procedures (average 1.5/year) were required for management of recurrent symptomatic FFVA

Table 3 Interventional radiology management of fast flow vascular anomalies: number of embolization procedures, approach, agent, and complications

Patient	Embolization procedures total number (number/year)	Approach and agent (number of procedures)	Complication
1	24 (1.5)	TAalc (5), TAg glue (3), TAonyx (4), Palc (2), Pglue (4), Ponyx (1), RTVcoil (1), RTVonyx (1), Pplug (1), Pcoil (1), PBleo (1), PSTS (2), venous PTA (3), and venous stent (2)	Loss of two toes due to intra-arterial sclerosant migration, left subclavian vein stenosis due to glue migration
2	6 (1.2)	TAalc (2), TAg glue (2), TAonyx (2), Palc (2), Pglue (1), Ponyx (1), Pplug (1), and Pcoil (1)	
3	4 (0.6)	TAalc (1), TAg glue (2), and Ponyx (1)	
4	4 (2)	TAalc (2), TAg glue (2), TAonyx(1), Pglue (1), and Ponyx (3)	

Abbreviations: Palc, percutaneous alcohol; PBleo, percutaneous bleomycin; Pcoil, percutaneous coil; Pglue, percutaneous n-butyl cyanoacrylate (glue); Ponyx, percutaneous Onyx; Pplug, percutaneous Amplatzer plug; PSTS, percutaneous sodium tetradecyl sulfate; PTA, percutaneous transluminal angioplasty; RTVcoil, retrograde trans-venous coil; RTVonyx, retrograde trans-venous Onyx; TAalc, trans-arterial alcohol; TAg glue, trans-arterial n-butyl cyanoacrylate (glue); TAonyx, trans-arterial Onyx.

for a total of 4 to 24 procedures per patient. The number of embolization procedures, approach, agent, and complications are outlined in ►Table 3. Pain related to FFVA responded well to embolization of arteriovenous shunts. However, pain secondary to the PTEN hamartoma responded poorly to percutaneous sclerosant injection of PTEN hamartoma. One patient (patient 1) had migration of sclerosant into digital arteries during percutaneous intratumoral injection of 3% sodium tetradecyl sulfate for management of recurrent foot pain. This led to ischemic necrosis and auto-amputation of fourth and fifth toes. During transarterial injection of glue in a left chest wall vascular anomaly in the same patient, there was migration of glue into the proximal subclavian vein resulting in venous stenosis and worsening venous hypertension of the left upper extremity. This was subsequently managed with angioplasty and stent placement.

Discussion

PTEN hamartoma tumor syndrome was recently described to encompass syndromes with overlapping phenotypes that share a germline mutation in the PTEN gene.^{1–3} Kurek et al introduced the term PTEN hamartoma of soft tissue for a unique finding of infiltrative intramuscular lesions containing fat, hypertrophic nerves with increased proliferation of periaxonal spindled cells, and serpiginous vessels.⁶ The authors noted that patients with PHOST presented with pain and swelling before the age of 15 years with intramuscular lesions most commonly in the lower extremity. Similarly, three-fourth patients in the present study had lower extremity intramuscular lesions that presented with pain and swelling in early childhood. One patient had the same clinical presentation, but affecting the upper extremity. The findings of heterogeneity, infiltrative nature, structural disorganization, and excess fat described by Kurek et al were also seen in the present study. In addition, the present study

demonstrates temporal evolution of these lesions: (1) enlargement of PTEN hamartoma on ultrasound and MRI with extension into contiguous muscle and subcutaneous fat, (2) development of new FFVA within existing PTEN hamartoma, and (3) development of new non-contiguous PTEN hamartoma and FFVA.

Similar to sonographic findings of PTEN hamartoma reported by Johnson and Navarro, all patients in the present study demonstrated heterogeneous hyperechoic disorganized muscle containing a cluster of high velocity vessels.¹³ Regarding angiographic findings,^{8,14} Tan et al divided vascular anomalies into arteriovenous, arterioleovenous, and arteriole-venulosis and described disproportionate dilatation of the proximal draining veins as a unique feature of FFVA in patients with PHTS.⁸ In addition to these features, one patient in the present study developed segmental-beaded arterial ectasia and large side-to-side fistula with the adjacent deep vein during follow-up. This resulted in large volume arteriovenous shunting with steal phenomenon that responded to transvenous occlusion of the arteriovenous communication.

Management of FFVA in patients with PTEN hamartoma is challenging and requires a multidisciplinary approach. Since patients present with recurrent pain and swelling, addressing the chronic pain is a critical component of their care. Understanding the mechanism of pain is crucial as therapy could target the trigger without having a universal recipe. Pain may be related to steal phenomenon from arteriovenous shunting (ischemic pain) and responds well to embolization. It may also be caused by the actively proliferating hamartoma secondary to presence of hypertrophic nerves or to mass effect on the surrounding tissues. Other benign tumors that are a hallmark of PTEN hamartoma tumor syndrome—trichilemmomas and oral papillomas—are not routinely associated with pain.^{1,2}

PTEN is a natural inhibitor of the mTOR pathway, and when the gene is mutated (inactivated) or deleted, the pathway is overly active inducing pathogenic proliferation

usually of mesenchymal elements. Sirolimus is an mTOR inhibitor that if administered daily regains some control over the downstream elements with resulting antiproliferative and antiangiogenic properties. As described in previous studies, PTEN hamartomas in the present study became softer and less painful and showed improved function of the affected region during administration of sirolimus.⁹ It did not however prevent increase in the size of the hamartoma or development of new FEVA. The medication had few side effects and was generally well tolerated during long-term administration. Introducing medical therapy with sirolimus improved pain and, thus, the quality of life in all patients in the present study. There was however recurrence of pain whenever the medication was discontinued, perhaps due pathologic proliferation from reactivation of the mTOR pathway. It is known that sirolimus does not have cytotoxic effect and is unable to reduce the size of an already formed arteriovenous malformation that is best addressed with IR procedures.

The goal of IR procedures is to obliterate abnormal arteriovenous communications, to improve perfusion to distal tissues, and to alleviate pain from steal phenomenon. The approach to treatment has to be tailored according to the angioarchitecture and ability to access the arteriovenous communications. The standard approach to management of congenital arteriovenous malformations is useful and applicable to FFVA in patients with PHTS.^{15,16} In the present study, the complexity of angioarchitecture required the use of transarterial, transvenous, and direct percutaneous approaches using several embolic agents and sclerosants during each procedure.¹⁶ The largest and most distal arteriovenous communications were occluded first to improve distal perfusion and to alleviate pain from steal phenomenon. The dilated ectatic proximal draining veins of FFVA served as a useful target for retrograde¹¹ or percutaneous transvenous embolization that was performed in three patients resulting in complete resolution of pain. In addition to occlusion of FFVA, direct percutaneous interstitial injection of sclerosant into the PTEN hamartoma was used in this study. Although this was technically successful during two procedures, the clinical success in terms of pain response was limited, and there was inadvertent migration of sclerosant into the digital arteries during a third procedure. Since PTEN hamartoma contains multiple abnormal vessels, this approach should be used with caution. Occlusion of larger arteriovenous communications had the best clinical response, but there was always recurrence of pain requiring repeated IR procedures alongside medical management.

Due to the intramuscular location of these tumors, physical therapy plays an important role in maintaining muscle strength, range of motion, and preventing contractures after surgical and IR procedures. Surgical excision has a limited, if any, role in the management of these patients.¹⁰

In conclusion, FFVA in PHTS present with recurrent pain requiring life-long management with a multi-disciplinary team. Pain due to FFVA responds to embolization, and that due to PTEN hamartoma of soft tissue responds to sirolimus.

Long-term combined use of IR procedures and medical therapy can improve the quality of life, but does not prevent disease progression. A comprehensive evaluation of the PHTS patient, identification of pain triggers, and targeting of all elements contributing to the symptoms are essential for success of therapy.

Disclosures

None of the authors has any disclosures.

Conflicts of Interest

None.

References

- 1 Hobert JA, Eng C. PTEN hamartoma tumor syndrome: an overview. *Genet Med* 2009;11(10):687–694
- 2 Eng C. PTEN: one gene, many syndromes. *Hum Mutat* 2003;22(03):183–198
- 3 Ngeow J, Sesock K, Eng C. Clinical implications for germline PTEN spectrum disorders. *Endocrinol Metab Clin North Am* 2017;46(02):503–517
- 4 Pilarski R, Burt R, Kohlman W, Pho L, Shannon KM, Swisher E. Cowden syndrome and the PTEN hamartoma tumor syndrome: systematic review and revised diagnostic criteria. *J Natl Cancer Inst* 2013;105(21):1607–1616
- 5 Roche AF, Mukherjee D, Guo SM, Moore WM. Head circumference reference data: birth to 18 years. *Pediatrics* 1987;79(05):706–712
- 6 Kurek KC, Howard E, Tennant LB, et al. PTEN hamartoma of soft tissue: a distinctive lesion in PTEN syndromes. *Am J Surg Pathol* 2012;36(05):671–687
- 7 Chism CB, Crawford L, Tchakarov A, Al-Ibraheemi A, Beckmann NM. PTEN hamartoma of the soft tissue: the initial manifestation of an underlying PTEN hamartoma tumor syndrome in a 4-year-old female. *Skeletal Radiol* 2017;46(11):1591–1595
- 8 Tan WH, Baris HN, Burrows PE, et al. The spectrum of vascular anomalies in patients with PTEN mutations: implications for diagnosis and management. *J Med Genet* 2007;44(09):594–602
- 9 Iacobas I, Burrows PE, Adams DM, Sutton VR, Hollier LH, Chintagumpala MM. Oral rapamycin in the treatment of patients with hamartoma syndromes and PTEN mutation. *Pediatr Blood Cancer* 2011;57(02):321–323
- 10 Sharabi SE, Koshy JC, Hollier LH Jr. Multiple, recurrent, refractory vascular malformations as the primary presenting feature of a PTEN mutation. *Pediatr Dermatol* 2011;28(04):466–467
- 11 Matsuhisa A, Kishino M, Nakadate M, Kudo T, Inoue Y, Tateishi U. Embolosclectomy by the transvenous approach for lower extremity arteriovenous malformation in Cowden syndrome: a case report. *Ann Vasc Dis* 2016;9(01):66–69
- 12 Takaya N, Iwase T, Maehara A, et al. Transcatheter embolization of arteriovenous malformations in Cowden disease. *Jpn Circ J* 1999;63(04):326–329
- 13 Johnson CM, Navarro OM. Clinical and sonographic features of pediatric soft-tissue vascular anomalies part 2: vascular malformations. *Pediatr Radiol* 2017;47(09):1196–1208
- 14 Turnbull MM, Humeniuk V, Stein B, Suthers GK. Arteriovenous malformations in Cowden syndrome. *J Med Genet* 2005;42(08):e50
- 15 Cho SK, Do YS, Shin SW, et al. Arteriovenous malformations of the body and extremities: analysis of therapeutic outcomes and approaches according to a modified angiographic classification. *J Endovasc Ther* 2006;13(04):527–538
- 16 Gilbert P, Dubois J, Giroux MFSG, Soulez G. New treatment approaches to arteriovenous malformations. *Semin Intervent Radiol* 2017;34(03):258–271