CASE REPORT

Assessment of PTEN-associated vascular malformations in a patient with Bannayan–Riley–Ruvalcaba syndrome

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Accepted 14 June 2016

SUMMARY

Misdiagnosis of phosphatase and tensin homologue hamartoma syndromes is common. Correct diagnosis has a relevant impact on patients, as the risk of malignancies is high and treatment options are limited. We report the case of a 24-year-old man who presented with symptomatic vascular intramuscular lesions of the left forearm and right calf, macrocephaly, post Hashimoto thyroiditis, a multicystic intracranial paratrigenal lesion, lentiginous hyperpigmented maculae on the foreskin and multiple skin lesions. MRI showed extended fibrofatty changes and malformed vessels in the forearm and calf lesions, also, arteriovenous shunting was present in these lesions. The patient had been treated by embolisation and surgically in the past, with limited results. A multidisciplinary assessment and genetic counselling were undertaken and a surveillance programme was initiated. Treatment options of the symptomatic vascular lesions include excision or possibly cryoablation. Physiotherapy to prevent progression of the contractures should be initiated meanwhile.

BACKGROUND

There is a high risk of malignancies in patients with phosphatase and tensin homologue (PTEN) hamartoma syndromes (PHTS). Correct diagnosis and the consecutive start of surveillance programmes for these patients and affected relatives are important. Misdiagnosis in patients with PTEN hamartoma tumour syndrome (PHTS) is still common, even in academic hospitals.

CASE PRESENTATION

Physical examination

A 24-year-old patient presented with symptomatic intramuscular vascular lesions of the left forearm and right calf. As a result of increasing pain and an equinus contracture of the right foot, he was unable to walk properly (figure 1). Overgrowth of the right calf, and lentiginous maculae on the foreskin and penis (figure 1) were apparent on physical examination. The patient's head circumference was 62 cm; however, his height was 170 cm, for which the normal centile for adult head circumference is >97. The multiple cutaneous lesions as seen in figure 1 were clinically consistent with trichilemmoma, which was not confirmed by biopsy.

Personal history

A macrocephaly had been present and recognised in this patient since birth, however, no explanation had

been found. The patient's height was 51 cm as a newborn and head circumference 38.5, with an according centile of >97. A haemangioma was first recognised on his forehead at 18 months, and another emerged at 4 years, which was excised. At the age of 7 years, his right leg swelled suddenly and had caused him pain ever since. He had undergone 3 months of hospitalisation for further examinations, with no explanation found for the swelling.

The patient had been seen in various hospitals and had been treated for Lyme's disease—which was thought to be the underlying reason for his symptoms—as well as for other diseases, including Hashimoto's thyroiditis.

The patient had learning difficulties in school and could not concentrate for long periods. After passing out of school, he had found it difficult to find a job. He currently worked as a warehouse clerk.

Family history

The patient's grandfather had two haemangiomas excised. His mother and sister also had haemangiomas excised and had multiple lipomas. The mother also had macrocephaly. His paternal grandmother had died aged 42 years due to an aggressive tumour.

INVESTIGATIONS

Colour coded duplex sonography (CCDS) showed fibrofatty changes in the calf and forearm muscles, with multiple abnormal arterial and venous vessels (figure 2), compared with normal muscle (figure 2). Malformed veins and arteries were present (figure 2) with apparent signs of arteriovenous shunting as the arterial inflow as well as the venous outflow were increased with an arterialised signal in the common femoral vein (figure 2). MRI confirmed extended fibrofatty changes and malformed vessels (figure 3). Fast flow within the lesion with relevant arteriovenous shunting was confirmed angiographically. A multicystic intracranial paratrigenal lesion was found on MRI of the brain.

Sequencing of the PTEN gene revealed a heterozygote missense mutation (p.D24Y), confirming the clinical diagnosis of Bannayan–Riley–Ruvalcaba syndrome (BRRS).

DIFFERENTIAL DIAGNOSIS

Other PTEN hamartoma syndromes such as Cowden syndrome (CS) or Proteus-like syndrome show overlapping clinical and imaging features.

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To cite: Anusic S, Clemens RKJ, Meier TO, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-215188

Figure 1 Clinical findings. Hyperplasia of right calf combined with equinus contracture due to shortening of the muscle caused by fibrotic changes of the musculature (arrow) (A). Skin lesion clinically consistent with trichilemmoma. These may be present along with other dermal lesions such as acral keratosis, papillomatous lesions or mucosal lesions (B). Penile freckling of glans and scrotum (arrows), the typical finding in male patients with Bannayan–Riley–Ruvalcaba syndrome (C).

Figure 2 Colour coded duplex sonography. (A and B) B-mode: diffuse hyperechogenic changes and loss of structure in affected muscle (A, arrows) compared with normal muscle (B). B-mode: abnormal, enlarged veins with slow flow within the lesion (arrow) (C). Colour-mode: abnormal, enlarged artery within the vascular lesion (arrow) (D). (E and F) Colour coded duplex sonography performed in the common femoral artery (E) showing continuous antegrade diastolic flow as evidence of distal arteriovenous shunting, and arterial pulsatile backflow in the common femoral vein, accordingly (F).

Figure 3 T2-weighted fat-saturated MR showing enlargement of the calf and extensive fibrofatty changes of the right calf M. gastrocnemius and M. soleus (arrows) (A). Abnormally formed venous vessels within the lesion (arrows) (B). (C and D) Extensive fibrofatty changes of the muscle. Note the amount of fat seen in the T1-weighted non-fat-saturated image (D) (arrows).

Macrocephaly may also be caused by an increase of cerebrospinal fluid, blood or bone hypertrophy. Trichilemmomas are often reported in association with severe neoplasms. The diagnosis of trichilemmoma needs to be proven histologically.

TREATMENT

The symptomatic intramuscular lesion of the right calf was treated with multiple transarterial embolisations. The contracture of the calf was treated conservatively with physiotherapy. The symptomatic intramuscular lesion of the left forearm was planned for excision. In these cases, compression stockings can be worn if this reduces symptoms. Basic medical treatment is limited to painkillers. Sirolimus, an mammalian target of rapamycin-inhibitor, is sometimes used in patients with complex vascular malformation. This may be an option on a case to case basis but it is an off-label use and the duration of the use is unclear.

OUTCOME AND FOLLOW-UP

The pain in the right calf improved after the embolisations, while the contracture worsened. This might have been the result of nerve damage (the pain improvement) and muscle damage. Alternately, natural progression of the contracture may have been the reason for the worsening of the contracture. The patient underwent genetic counselling, which resulted in the following screening programme:

- ▶ Yearly thyroid ultrasound and skin check with physical examination;
- ▶ Colonoscopy beginning at age 35 years;
- ▶ Frequent (every 2 years) renal imaging with ultrasound or MRI beginning at age 40 years.

Given the autosomal dominant inheritance of the syndrome, all first-degree relatives should be evaluated and tested.

DISCUSSION

PTEN is a protein encoded by the PTEN gene. It is a tumour suppressor gene.¹ More than 70 mutations of the PTEN gene are known today. These mutations cause the gene to produce

non-functioning proteins or even cause a complete loss of transcription. The defective protein is no longer able to signal abnormal cells to die or to control cells to divide, which prevents abnormal cells dying. The loss of function of the protein of the PTEN gene, caused by somatic mutations, which have to be clearly differentiated from germline mutations, are found in multiple cancers, including glioblastoma, endometrial cancer, breast cancer, thyroid cancer and prostate cancer.^{2–3} PTEN-germline heterozygous mutations are found in BRRS and CS.⁴ Usually, an autosomal dominant heritage is apparent, but de novo mutations are also possible.⁵ Together with PTEN-related Proteus syndrome (PS), and Proteus-like syndrome, these four diseases are included in the PHTS by some authors.^{6–7} There is an ongoing discussion to clarify whether true PS should be diagnosed in patients with PTEN-mutations and therefore not be included in PHTS.^{8–11}

If a PTEN pathogenic variant is diagnosed by genetic testing, the gene-related name, PHTS, should be used.

Characteristic findings of BRRS (OMIM 153480) are macrocephaly, developmental delay, penile freckling in males, benign lesions of primarily mesodermal origin, which include lipomas, and vascular lesions that are mainly found intramuscularly. Other important features are gastrointestinal polyposis and café-au-lait spots. Overlapping clinical and imaging features of BRRS and CS in one family are possible.¹²

CCDS is the choice for initial assessment of vascular lesions in PHTS/BRRS; it provides information about the degree of vascularity of a lesion and the ability to differentiate between vascular tumours and vascular malformations. CCDS also reveals high-flow and low-flow characteristics without the need for contrast injection or angiography. It can be used for first assessments, as well as for follow-ups.¹³ CCDS is also used to monitor the shunt volume if a high-flow lesion is treated. Disadvantages of CCDS are a limited field of view, restricted penetration and operator dependency. MRI is often needed additionally and is used for follow-ups to monitor lesion size.¹⁴ Angiography is performed to describe flow characteristics and to plan interventions.

Misdiagnosis of vascular lesions found in PTHS is common. Diagnosis in many of the published case reports needs to be questioned for accuracy, as biopsies are often not performed or, if carried out, misinterpreted. A common misdiagnosis is haemangioma.^{15 16} This may lead to wrong medical treatment, with β blockers, for example. Other diagnoses found in the literature include arteriovenous malformation.¹⁷ This diagnosis leads to arterial embolisations, which may well reduce the amount of shunting, but may also worsen the contracture through destruction of muscle, and which do not target the fibrofatty changes that form the main body of the lesion. Also, lymphatic malformations, or 'lipolymphangiohaemangiomas', have been diagnosed.^{18 19} These histopathologically made diagnoses reflect the heterogeneity of the tissue found in the same vascular lesion in patients with PTHS. These vascularised lesions in PTHS can be distinctively characterised as PTEN hamartomas of soft tissue (PHOST). Kurek *et al*²⁰ found predominately intramuscular fast-flow vascular lesions in their series on patients with PHTS. PHOST feature an overgrowth of mingled soft tissue elements formed from dense adipose and fibrous tissues, with abnormal blood vessels of various types. This combination makes PHOST distinctive from other intramuscular vascular lesions. The infiltrative intramuscular involvement is an imaging characteristic of vascular anomalies in patients with PTEN hamartoma syndrome, but is also found in patients with syndromes such as congenital lipomatous overgrowth with vascular, epidermal and skeletal anomalies or the fibro-adipose vascular anomaly, where the fibrofatty changes form the main body of the lesion.^{21 22}

If the intramuscular lesions are small, total resection is the best treatment option. The diseased muscle is mostly non-functional and only a burden for the patient. This option is limited by the size of the lesion and other involved surrounding structures such as nerves. Transarterial embolisation may improve pain by destroying nerves, but has no relevant effect on size and contracture. Ethanol embolisation might even destroy vital muscle, leading to fibrosis, with consecutive contracture of the muscle, as the treatment is not selective. Cryoablation can be an option, but has to be discussed on a case to case basis; also, available data are limited to case reports.

Psychological impact on patients is high as they have an increased risk of malignancies and may pass the mutation on to their children.

The involvement of multiple different localisations and organs leads to a high cumulative lifetime risk for various cancers, especially breast cancer and thyroid cancer.²³ No long-term follow-up of these patients has been reported yet. There is an ongoing controversy over whether these syndromes should be closely monitored for thyroid, breast, endometrial and renal malignant transformation. Especially in BRRS, the risk of malignant transformation seems to be lower than in CS or PS.

Patient's perspective

I was discouraged for a very long time. I had several consultations and operations, without ever getting an answer for what I had. As this went on for many years, it was a huge relief for me to finally get a diagnosis. I am worried about the possibility of cancer and, if I do get it, I hope the surveillance programme will detect it. I do not know yet if my children will be affected. I really hope that research will maybe help others 1 day.

Learning points

- ▶ Misdiagnosis of vascular malformations and complex syndromes is still common.
- ▶ Existence of multiple diseases in a patient should raise awareness of a syndrome. An internet search including only some features (ie, penile freckling and Hashimoto's thyroiditis) may lead to the correct diagnosis.
- ▶ Penile freckling is the key clinical feature in Bannayan–Riley–Ruvalcaba syndrome in male patients.
- ▶ Colour coded duplex sonography (CCDS) is still the choice for initial assessment: it provides information about the degree of vascularity of a lesion and the ability to differentiate between vascular tumours and vascular malformations. CCDS also reveals the high-flow and low-flow characteristics without the need for contrast injection or angiography. It can be used for first assessments, as well as for follow-ups.
- ▶ Even if treatment options in phosphatase and tensin homologue hamartoma syndromes are limited, an appropriate surveillance programme that includes dependents should be initiated after diagnosis.

Nonetheless, many authors recommend the treatment and follow-up protocol in BRRS as recommended by the National Comprehensive Cancer Network Monitoring, to detect malignancies at the earliest and therefore most treatable stage.²⁴

Contributors All authors listed have contributed sufficiently to the case report to be included as authors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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