OPEN ACCESS

Parkes-Weber syndrome in the emergency department

Raj Patel,[1] Edward James Durant ,[2,3] Robert Freed[4]

[1]Touro University CA COM, Vallejo, California, USA
[2]Emergency Department, Kaiser Permanente, Modesto, California, USA
[3]Department of Clinical Science, Kaiser Permanente Bernard J Tyson School of Medicine, Pasadena, California, USA
[4]Department of Interventional Radiology, Kaiser Permanente, Sacramento, California, USA

Correspondence to
Dr Edward James Durant; edward.durant@gmail.com

Accepted 2 September 2021

To cite: Patel R, Durant EJ, Freed R. *BMJ Case Rep* 2021;**14**:e241649. doi:10.1136/bcr-2021-241649

SUMMARY

This case report describes a 20-year-old woman presenting to the emergency department (ED) with unilateral leg swelling. After multiple visits to the ED and workups with rheumatology, dermatology, interventional radiology and genetics, she was finally diagnosed with Parkes-Weber syndrome. The purpose of this case report is to illustrate the common and uncommon presentations, mimickers and work-up of Parkes-Weber syndrome as well as provide a brief overview of vascular malformations in general.

BACKGROUND

Parkes-Weber syndrome is a rare genetic disease with an unknown prevalence presenting with pathological capillary malformations and arteriovenous malformations affecting the same limb.[1] The aetiology is due to a spontaneous or inherited RASA1 gene mutation involved in the development of the vascular system.[1] At birth or during childhood, the capillary malformations clinically present as portwine stains, whereas the arteriovenous malformations present as hemihypertrophy, resulting in length/circumference discrepancies and spontaneous swelling associated with pain. The most significant life-threatening complication is high-output heart failure secondary to the arteriovenous malformations, resulting in cardiomegaly and pulmonary oedema.[2]

Another syndrome commonly confused with Parkes-Weber syndrome is Klippel-Trenaunay syndrome, as both are associated with capillary malformations (portwine stains), hemihypertrophy and a deep tissue malformation. They can be distinguished, however, by the difference in appearance of the portwine stains and by the type of deep tissue malformations. The portwine stains of Parkes-Weber syndrome are salmon-coloured, in contrast to dark purple in Klippel-Trenaunay syndrome[3 4]; and the deep malformations of Parkes-Weber syndrome are arteriovenous malformations, whereas those in Klippel-Trenaunay syndrome are venous malformations.[1] Therefore, although both syndromes have similarities, the symptoms and treatments are vastly different.

CASE PRESENTATION

A 20-year-old woman with no relevant previous medical history presented to the emergency department (ED) with 1 day of painful, acute worsening of her chronic left thigh swelling without an identifiable trigger. She denied additional symptoms, trauma, personal and family history of thrombosis or coagulopathy, and tobacco or illicit substance use. A routine workout 2 days prior was unchanged from her usual described intensity. The pain was described as 'tightness', which was relieved by rest and aggravated by movement. The patient reported that her chronic asymmetry was never investigated by previous physicians because it was only slightly wider in girth and non-painful since childhood. Her only prescribed medication was a levonorgestrel intrauterine device, and family history was significant for ulcerative colitis and coronary artery disease.

The physical examination revealed her to be in no acute distress with normal vital signs. Relevant findings included a left thigh, which was roughly double the circumference, but the same length, as the right. Otherwise, both thighs had soft compartments without erythema, crepitus, warmth or tenderness to palpation (figure 1). Her neurovascular function was normal bilaterally, there was no pitting oedema or calf swelling, and no discomfort was noted behind the knee on forced dorsiflexion. Finally, no urine colour changes were noted. All other findings were either normal or not clinically relevant. Notably, capillary malformations in the patient's left thigh had been present since birth but were not noted on the treating physician's examination.

INVESTIGATIONS

The initial workup revealed a normal complete blood count, normal basic metabolic panel (including calcium, magnesium and phosphate), negative pregnancy test (qualitative human chorionic gonadotropin), elevated d-dimer at 3.25 μg/mL (normal <0.49 μg/mL) and creatine kinase at 7697 U/L (normal <200 U/L). Other studies such as uric acid level, liver function tests, prothrombin time, activated partial thromboplastin time, serum aldolase and lactate dehydrogenase were not ordered at the attending physician's discretion. The clinician ordered a venous Doppler ultrasound of the lower extremity and consulted nephrology and orthopaedics for additional recommendations.

The lower extremity ultrasound revealed patent, compressible, bilaterally symmetric femoral and popliteal veins. It also showed soft tissue oedema in the medial left thigh. Nephrology recommended serial creatine kinase measurements to ensure downtrending levels, while the orthopaedic surgeon recommended a left femur radiograph and lower extremity MRI with and without contrast (figure 1) to evaluate for muscle or tendon tears or evidence of myositis.

The radiograph showed no acute fracture with normal femur morphology. MRI results showed left thigh subcutaneous and fascial oedema with biceps femoris and semitendinosus muscle hyperintensity (figure 2). There were no fluid collections or mass lesions and the neurovascular bundle was intact.

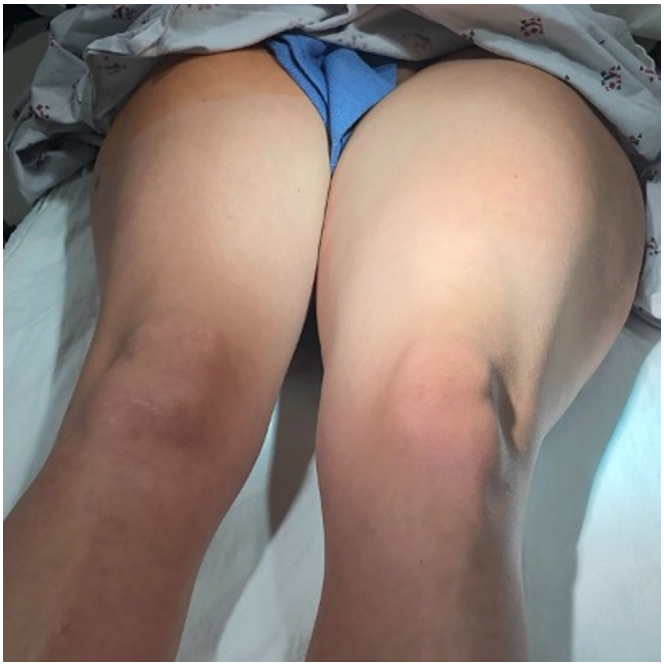

Figure 1 Hemihypertrophy of the left lower extremity.

None of the studies was noted to show evidence of arteriovenous (AV) malformation on the radiologist's read.

DIFFERENTIAL DIAGNOSIS

The treating clinician's differential diagnosis included rhabdomyolysis, deep venous thrombosis, compartment syndrome, necrotising fasciitis and cellulitis. Given that the patient had no known history of chronic medical conditions, no congenital conditions were considered in the differential diagnosis.

Rhabdomyolysis was considered the most likely diagnosis due to elevated creatine kinase levels, acute onset symptoms and recent exercise. Deep venous thrombosis was ruled out with venous Doppler ultrasound. Compartment syndrome was ruled out with a normal femur radiograph. Necrotising fasciitis and cellulitis were ruled out by physical examination and lack of fluid collections on MRI.

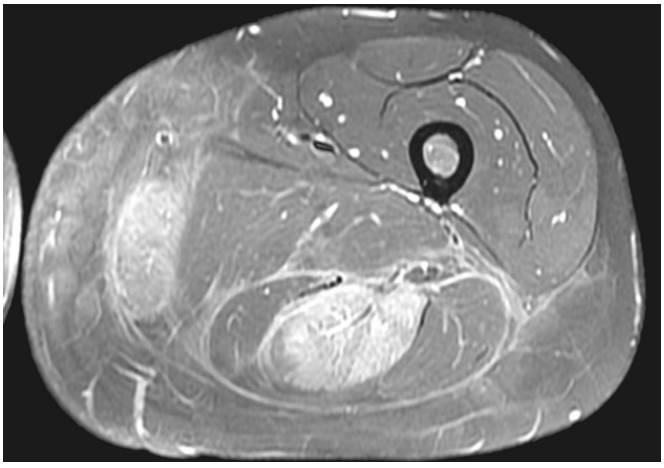

Figure 2 Edematous biceps femoris and semitendinosus muscle with extension along the fascia and into the subcutaneous tissue.

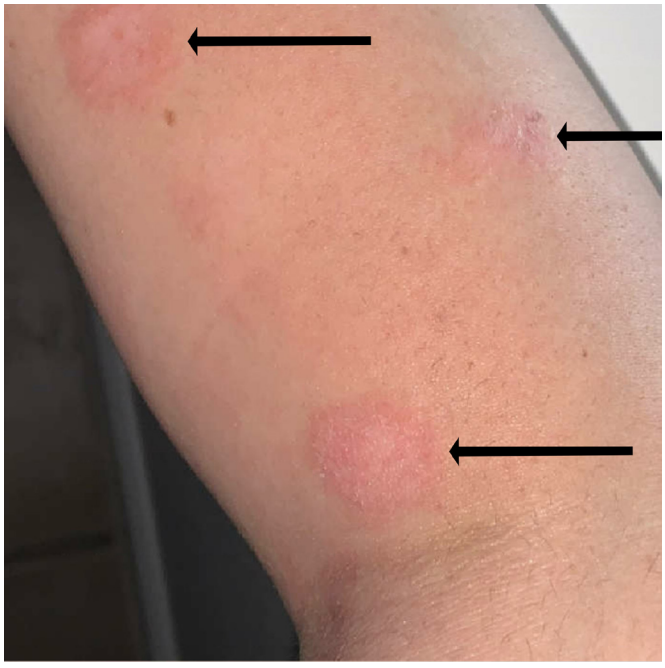

Figure 3 Capillary malformations assessed as 'birthmarks' of the left lower extremity (black arrows).

TREATMENT

The patient was then received a 30 mL/kg bolus of normal saline to prevent acute kidney injury and 1000 mg IV acetaminophen. Adequate pain control was achieved with 4 mg IV morphine.

OUTCOME AND FOLLOW-UP

After discussion with orthopaedics and nephrology and an extended stay in the ED, the emergency physician and consultants determined that the patient was safe for discharge home with the diagnosis of rhabdomyolysis and a plan to follow-up with internal medicine. The reasoning included definitive exclusion of life-threatening alternative diagnoses, stable patient presentation for greater than 11 hours with improvement in swelling and pain, creatine kinase level downtrend from 7697 U/L to 1800 U/L and the ability to reliably follow-up within 2–3 days.

Over the next 6 months, she presented to the ED three times with similar reports while intermittently being seen by multiple specialists as an outpatient. In rheumatology, autoimmune diseases including myositis were ruled out. Dermatology assessed large 'birthmarks' on her left leg (figure 3) and referred her to interventional radiology for suspected vascular malformations. The venogram performed by interventional radiology revealed arteriovenous fistulas in the left thigh (figure 4). Parkes-Weber was then proposed as the diagnosis, and a genetic analysis revealing a RASA1 variant (Chr5(GRCh37)g.86659154_86659158del) confirmed the diagnosis. She continues to have regular follow-up with her oncologist to monitor for potential complications such as heart disease with echocardiograms, limb ischaemia with symptom reviews and aneurysms with MRIs.

DISCUSSION

Parkes-Weber syndrome typically presents in infancy or childhood with characteristic features prompting further investigation. This atypical case in a young adult required a work-up for infectious, traumatic and thrombotic mimickers of extremity swelling. Additionally, the general lack of knowledge in the

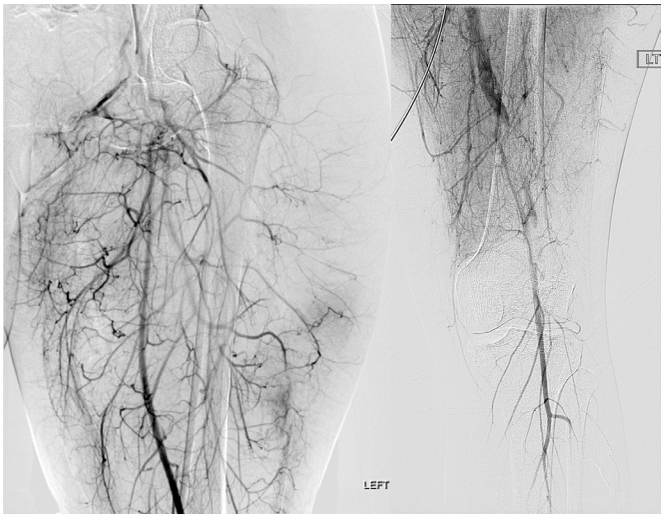

Figure 4 The left lower extremity, specifically the thigh is affected with what looks like a diffuse type shunt. There is an obvious demarcation with the lower leg which is not affected.

medical field regarding vascular anomalies led to consistent failures across multiple specialties to recognise symptomatology and physical examination findings that could have resulted in early referral to the appropriate specialty group. This in turn resulted in a delay in care, repeat ED visits and significant emotional distress for the patient.

In the ED, Parkes-Weber syndrome is an important diagnosis to understand as these patients require extra attention when presenting with an otherwise common chief report. The arteriovenous malformations can occur in any location, including the brain, therefore, mild symptoms can lead to potential disasters such as subarachnoid haemorrhage. Additionally, the finding of heart failure (due to the arteriovenous malformations) occurring in an atypical demographic can result in increased mortality due to delayed diagnosis. Finally, as the disease is found primarily in infancy and childhood, it complicates the already specialised emergency care needed for this population.

An important function of emergency physicians is identifying the appropriate specialists to contact for consultations and referrals. Parkes-Weber syndrome is managed by an interdisciplinary group, such as a vascular anomalies clinic, which includes interventional radiologists, dermatologists, general surgeons, haematologists/oncologists and otolaryngologists. These specialty groups are the preferred consultants for Parkes-Weber syndrome emergency visits, especially if the patient is already under their care, and prior consult notes are available. Alternatively, interventional radiology can be contacted for an initial evaluation in the event that such a specialty group is unavailable.

In an undiagnosed and undifferentiated patient, such as this case, the ED workup is limited due to time constraints, patient load and availability of specialists. In these situations, it is acceptable to exclude life-threatening diagnoses, identify the relevant symptoms and physical examination findings and refer the patient to a specialty clinic for further workup. Therefore, although the diagnosis is unlikely to be made in the ED, there is a unique opportunity to identify it as a possibility and make an early referral to avoid a delay in care. A basic understanding of vascular malformations and their complications is needed to accomplish this.

It is important to recognise that vascular malformations have traditionally been poorly described, misclassified and misunderstood. This is presumably a result of low prevalence and a wide spectrum of appearances and anatomic locations. Additionally, in the author's experience, misclassification can often start with a radiology report using 'haemangioma' or 'arteriovenous malformations' as umbrella terms to describe any vascular anomaly. This error then propagates into clinical notes and persists throughout the medical record. The International

Patient's perspective

If I were to look at my life a few years ago, I never would have pictured what I have experienced or gone through medically and emotionally. For as long as I can remember I have been very happy and healthy with no medical issues. What started as random symptoms the morning of 31 May 2019 has become a lifelong diagnosis with a lot of attachments and 'what ifs'. For the first few months, I struggled getting anyone to see what I was seeing and feeling. I felt very defeated and 'crazy' for what I was experiencing, and the feelings only deepened the more and more I kept hearing 'we do not see anything wrong with you'. I saw countless specialists, had multiple procedures and had various forms of imaging yet no answer. Finally, my 'answer' came from an Interventional Radiologist who not only provided me a diagnosis but also discovered a medical issue I never knew I had, Parkes-Weber syndrome. Finally, after many months, I had someone who believed that something was wrong and fought to find an answer, something I never thought would happen. While the diagnosis was a relief to have, I soon discovered it came with a lot of baggage: countless doctors' visits, many forms of recurring imaging and lab work, chemotherapeutic drugs, experimental forms of treatment and the worst of all a lack of information. The lack of information surrounding my disease has not only affected me emotionally but also physically as well. I have watched myself get worse and worse as time passes all while not knowing necessarily why or how to stop it. Unfortunately, it is not just in the unknown, but my healthcare team as well. I have had to think about things I never wanted to think about at the age of 21 such as, a shortened life expectancy, the effects of chemo medications on my body, and even freezing my eggs to hopefully have the opportunity to have children 1 day. This disease has taken over my life both emotionally and physically. I am no longer the active, healthy and happy girl I was for 20 years. While this disease has turned my life upside down in many ways, I still hold hope that 1 day things will get better and with more information people like me with this disease can have a better and longer life that is not filled with barriers, fear and pain.

Learning points

- Parkes-Weber syndrome usually presents in infancy but can also present atypically later in life.
- The diagnosis of Parkes-Weber syndrome is important because it is associated with cardiac, neurological and vascular complications that can cause significant morbidity and mortality.
- The diagnosis of Parkes-Weber syndrome requires a high index of suspicion and a multidisciplinary approach.
- If Parkes-Weber syndrome is seen in the past medical history of a patient, an interdisciplinary vascular group or interventional radiology should be consulted.

Society for the Study of Vascular Anomalies has developed an applicable classification scheme for vascular anomalies. In general, however, vascular malformations can be classified as venous, lymphatic and arteriovenous.

Pure venous malformations are characterised by a low blood flow state complicated by deep venous thrombosis and thrombophlebitis with minimal risk of pulmonary embolism,.[5] The preferred acute treatment for these complications is a 10-day course of enoxaparin, but lifelong anticoagulation may be necessary for recurrent episodes. Other options for prevention of thrombosis are aspirin and compression stockings. Lymphatic malformations can result in infection of, or haemorrhage into, dilated lymphatic channels presenting with localised swelling and cellulitis.[6] Drainage is usually unnecessary as these may be managed with antiinflammatory medications, antibiotics and analgesics. It is important to re-emphasise that a serious outcome of arteriovenous malformations is high-output heart failure; additionally, as seen in this patient, they may also present with rhabdomyolysis secondary to ischaemia of the surrounding tissues. The heart failure can be treated acutely with diuresis, as traditional management with bi-level positive airway pressure, and nitrates may exacerbate the symptoms. Renal function may be protected with intravenous fluids in cases of rhabdomyolysis.

Of note, a similar case has been reported by Chagas *et al*.[7] Here, the authors compare and contrast Parkes-Weber syndrome and Klippel-Trenaunay syndrome through the presentation of two cases. The Parkes-Weber syndrome case is of particular importance, as it describes another undiagnosed patient in her 20s presenting with lower extremity limb disproportions, joint pain and claudication. Doppler ultrasound and magnetic resonance angiogram (MRA) were performed to confirm the presumed diagnosis of Klippel-Trenaunay syndrome, but instead revealed an arteriovenous fistula, which changed the diagnosis to Parkes-Weber syndrome. Although high-output heart failure is discussed as a complication, pulmonary manifestations such as thromboses and varicosities are also discussed. Finally, differential diagnoses including Proteus syndrome, neurofibromatosis type 1 and Sturge-Weber syndrome are noted to be considered alongside these syndromes.

The most important limitation of reports involving Parkes-Weber syndrome is the lack of information regarding the subject. Other cases have been described in the literature, which highlights the challenges in appropriately diagnosing this condition.[7] Common epidemiological points are both unidentified and underidentified including the aetiologies, risk factors, prevalence and outcomes. However, this is less relevant here as the aim of this report is to increase awareness of Parkes-Weber syndrome and vascular malformations that may be encountered in the emergency setting.

Contributors RP contributed to the conception and design of the work, literature review and analysis, drafting the article, critical revision of the article and final approval of the version to be published. EJD contributed to the conception and design of the work, literature review and analysis, drafting the article, critical revision of the article and final approval of the version to be published. RF contributed critical revision of the article, expert opinion and final approval of the version to be published.

Funding This study was funded by Kaiser Permanente.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Edward James Durant http://orcid.org/0000-0003-2039-2788

REFERENCES

1 ISSVA classification of vascular anomalies ©2018 International Society for the study of vascular anomalies. Available: issva.org/classification [Accessed 4 Aug 2020].
2 Bayrak-Toydemir P. Capillary Malformation-Arteriovenous Malformation Syndrome [Internet]. GeneReviews® [Internet]. U.S. National Library of Medicine, 2019. Available: https://www.ncbi.nlm.nih.gov/books/NBK52764/
3 Parkes Weber syndrome: MedlinePlus Genetics [Internet]. U.S. National Library of Medicine. National Institutes of Health, 2011. Available: https://ghr.nlm.nih.gov/condition/parkes-weber-syndrome
4 Klippel-Trenaunay syndrome: MedlinePlus Genetics [Internet]. U.S. National Library of Medicine. National Institutes of Health, 2016. Available: https://ghr.nlm.nih.gov/condition/klippel-trenaunay-syndrome
5 Behravesh S, Yakes W, Gupta N, *et al*. Venous malformations: clinical diagnosis and treatment. *Cardiovasc Diagn Ther* 2016;6:557–69.
6 Lymphatic Malformations [Internet]. NORD (National Organization for Rare Disorders), 2019. Available: https://rarediseases.org/rare-diseases/lymphatic-malformations/
7 Chagas CAA, Pires LAS, Babinski MA, *et al*. Klippel-Trenaunay and Parkes-Weber syndromes: two case reports. *J Vasc Bras* 2017;16:320–4.