Received: 6 March 2021 | Revised: 30 May 2021 | Accepted: 12 June 2021

DOI: 10.1002/ccr3.4527

CASE REPORT

Clinical Case Reports Open Access WILEY

Lymphangioma of the fetal neck within the PIK3CA-related-overgrowth spectrum (PROS): A case report

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Abstract

The delineation of the prenatal diagnostic key features of PIK3CA-related overgrowth spectrum disorders will assume a crucial part in future and a prenatal diagnosis of the causing mutations would provide physicians with a simplified interdisciplinary perinatal management.

KEYWORDS

cervical, congenital, fetal, lymphangioma, lymphatic malformation, neck, PIK3CA, PIK3CA-related-overgrowth-spectrum, prenatal

1 | INTRODUCTION

Congenital fetal neck tumors constitute exceedingly rare antenatal conditions. Prenatal diagnosis is usually straightforward by detailed sonographic examination. According to current literature, these lesions are categorized into different types.[1–3] The most frequently described subtypes of neck tumors comprise lymphangiomas, followed by teratomas and hemangiomas.[1] However, the exact incidence of lymphangiomas remains unclear. It varies considerably whether pre- or postnatal cohorts are analyzed. Prenatal data suggest an estimated incidence of up to 1 in 1000 live births.[2,4,5]

Although lymphangiomas are nonmalignant vascular malformations of the lymphatic system and histologically mostly benign, extensive and heterogeneous tumor masses may compress vital cervical structures, so the final prognosis has been reported to be poor.[1,2,6,7]

The clinical course of lymphangiomas is related to the type of lymphatic malformation and varies from a mild symptomatic that tends to regress spontaneously to an aggressively invasive growth into surrounding vital structures.[5] Spontaneous regression in the latter cases is unlikely, but possible.[4,8] By compressing phenomena, potentially life-threatening events may arise, if polyhydramnios or airway obstruction occur.[5,6,8,9]

Lymphatic malformations like lymphangiomas usually arise from the defective embryological development of primordial lymphatic structures.[3,8,10] Recent data revealed

that lymphangiomas receive their growth stimuli by activating missense mutations characterizing disorders with benign overgrowth, collectively known as PIK3CA-related-overgrowth-spectrum (PROS).[9,11–13]

PROS encompasses a group of disorders that are predominantly characterized by benign segmental overgrowth of several tissues with vascular and lymphatic malformations. Caused by heterozygous, mostly somatic mosaic-like pathogenic variants in the PIK3CA gene that arise postzygotically, affected patients may present with regional-located or multiple-located findings.[6,9,14,15] The clinical picture strongly depends on the embryonic stage in which the causative mutation occurred, as well as the tissue type affected by this mutation.[15] Specific somatic activating mutations in the phosphatidylinositol-3-kinase/AKT/mTOR (PI3K-AKT-mTOR) pathway lead to heterogeneous segmental overgrowth phenotypes.[14] The PIK3CA gene encodes the 110 kD catalytic alpha subunit (p110α) of the PI3K protein complex, a lipid kinase of the PI3K-AKT-mTOR pathway, a signaling pathway, which is crucially involved in the regulation of cell proliferation, metabolism, and survival as well as in angiogenesis. Hence, PI3K plays a key role in cell growth and division as well as cell migration and survival.[6,9,16] An altered activity of PI3K leads to uncontrolled cell division, and as somatic mosaics, these mutations may trigger the development of overgrowth syndromes with segmental growth of several tissues with venous as well as lymphatic malformations to varying degrees.[6,9,13,16]

Over the past years, cancer-associated PIK3CA mutations have been also reported to be responsible for a wide range of clinical benign overgrowth disorders.[6,17] Recent insights emphasize the topicality of PROS disorders.[9,13,18]

Regionally limited lymphangiomas developing within the context of PROS are scarcely mentioned in the literature, and there are almost no informative case reports. While the acronym PROS is an umbrella term for various clinical entities, even those entities themselves, like lymphangiomas, can morphologically resemble as a chameleon.[14]

In the present report, the prenatal and postnatal course of a fetus suffering from a huge cervical lymphangioma within the PROS will be delineated. We discuss the clinical picture to what is known from current literature and focus on the targeted multidisciplinary approach to establish the final confirmation of an activating missense mutation hotspot c.1633G>A;p.Glu545Lys identified by next-generation sequencing.

2 | CASE PRESENTATION

2.1 | Prenatal course and diagnostics

A 28-year-old woman, gravida 3, para 1, in the 28th week of pregnancy was referred to our prenatal diagnostic center due to the suspicion of a fetal neck tumor detected by prenatal ultrasound. The course of pregnancy was uneventful until the 28th week of pregnancy. The mother reported one prior spontaneous miscarriage and had no regular medication. The parents were of Caucasian origin and nonconsanguineous, and the family history was otherwise unremarkable. A detailed fetal anatomic ultrasound survey confirmed a fetal neck tumor with a dimension of 45 × 46 × 39 mm located at the anterior neck, presenting morphological features of a cystic-caverneous lymphohemangioma. The tumor extended from the right submandibular region across the front of the neck to the opposite side, with weak vascularization. The tumor was supposed to infiltrate the base of the mouth. Additionally, the mass could not be separated from the upper thoracic aperture (Figure 1A,B). With the exception of a polyhydramnios, no further sonomorphological abnormality of the fetus was detected. The fetus showed an appropriate growth with an estimated fetal weight of 1020 g corresponded to the 28th percentile. The parents decided against an amniocentesis. Subsequent ultrasound examinations within two to three months showed the growth of the tumor (73 × 68 × 41 mm), which was already strongly vascularized and now affecting the floor of mouth, but without identifying its entity beyond any doubt (Figure 1C,D and Video S1). The parents were interdisciplinary counseled together with neonatologists and pediatric surgeons. Magnetic resonance imaging (MRI) was performed, confirming the inhomogeneity as well as the extent of the tumor but was also unable to clarify the definite tumor entity.

2.2 | Postnatal neonatological intensive care, diagnostics, therapy, and diagnosis of PROS

A female infant was delivered weighing 3450 g (74th percentile), 49 cm length (27th percentile), and 35 cm head circumference (71th percentile) by cesarean section with neonatological standby of an ex utero intrapartum treatment (EXIT) procedure in 39th week of gestation (Figure 2A,B). The newborn adapted well and presented in good condition: APGAR 8/9/10, arterial umbilical cord pH 7.39. Initially, it required no active management and was immediately transferred to the neonatologist care unit. During inpatient stay, the infant underwent an extensive interdisciplinary neonatological intensive care with regular ultrasound and MRI follow-up (Figure 2C,D). The lymphangioma seemed to be stable. With intention of tumor regression as well as obtaining tissue, several sonographically controlled biopsies of the neck with multiple injections of Picibanil (OK-432) and the partial resection of areas of the tumor were performed. Attempting tumor size restriction with Propranolol, based on the histopathological suspicion of a hemangioma and the meanwhile significant

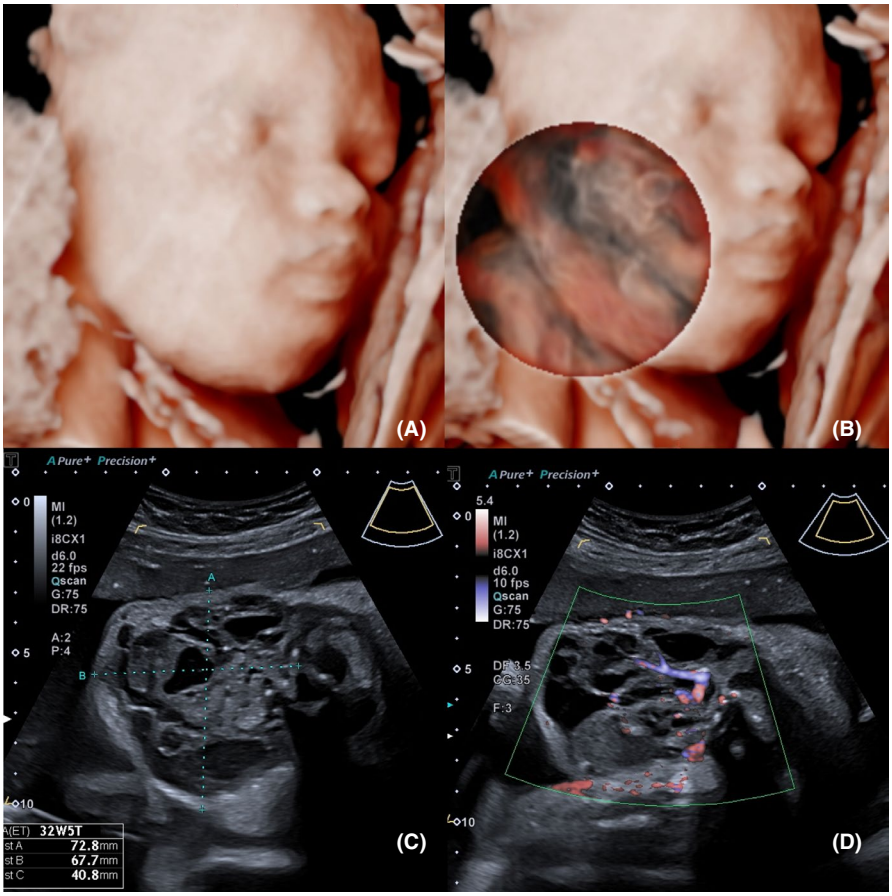

FIGURE 1 2D- and 3D-ultrasound imaging with Samsung UGEO WS80 Elite in 28th (A, B) and 33rd (C, D) week of gestation. (A) The tumor extends from the submandibular region to the upper thoracic aperture. (B) Internal structures of the lymphangioma on Crystal Vue™. (C) The lymphangioma presents as a multicystic, multiseptated, scattered hypoechoic structure with diffuse infiltration of its environment. The tumor mass appeared morphologically mostly as a lymphangioma impressed by solid components, similar to a teratoma. (D) Power Doppler shows diffuse arterial and venous vascularization, resembling aspects of a hemangioma.

Images from the Department of Prenatal Medicine and Gynecological Ultrasound, University Hospital Schleswig-Holstein, Campus Lübeck

tumor progression, failed. The histopathological findings and the clinical presentation of the tumor rather suggested a lymphangioma. In the meantime, an evaluation by ultrasound and MRIs of the neck showed a semicircular tumor extension, reaching cranially to the mastoid and intrathoracally to the carina with increasing infiltration of the base of the tongue and marked constriction of the cervical vessels without airway obstruction. With histopathological evidence of markers of the mTOR pathway, associated with a number of overgrowth disorders, a therapeutic approach with Sirolimus was initiated and resulted in a minimal size reduction. Nearly during the entire inpatient stay and despite an extensive interdisciplinary management, the etiology of the lymphangioma remained unclear and the conventional molecular genetic investigation a challenging process. To establish a final diagnosis, next-generation sequencing (NGS) was performed and subsequently resulted in the detection of the missense mutation c.1633G>A;p.Glu545Lys.

3 | DISCUSSION

In certain cases of congenital fetal neck tumors, establishing a definite prenatal diagnosis might be challenging or even impossible. Despite all advances in imaging techniques available today, it remains challenging to delineate the underlying cause of such etiologically heterogeneous tumors in utero. Both, the infant and physicians, as well as the parents, will benefit from the most accurate clinical and, if possible, molecular pathological classification of the etiology of the tumor in order to be able to plan further interdisciplinary treatment. If the final diagnosis in this case presented had been known earlier, a number of therapeutic approaches could have been avoided.

During fetal life, tumors of the neck tend to impair fetal swallowing, often resulting in polyhydramnios.[8] Another serious threat potentially arises from local compression phenomena.[6] Lymphatic malformations of the fetal neck with lymphangiomas constitute the most prevalent fetal neck mass.[1,2,4,8] In the last two decades, there were a number of attempts to classify these lesions according to their etiological origin,[8,10] morphological appearance,[5,10] histological features,[5,7] or postnatal course.[10] All these different classifications can coexist, and their characteristics occur side by side. A common and generally accepted classification of lymphatic malformations is merely based on histological criteria. There are four distinct histological types of lymphangiomas consisting of capillary or cavernous lymphangioma, cystic hygroma, and vasculolymphatic malformation.[7] However, Eivazi et al. stressed that this traditional histological classification is obsolete.[10] With

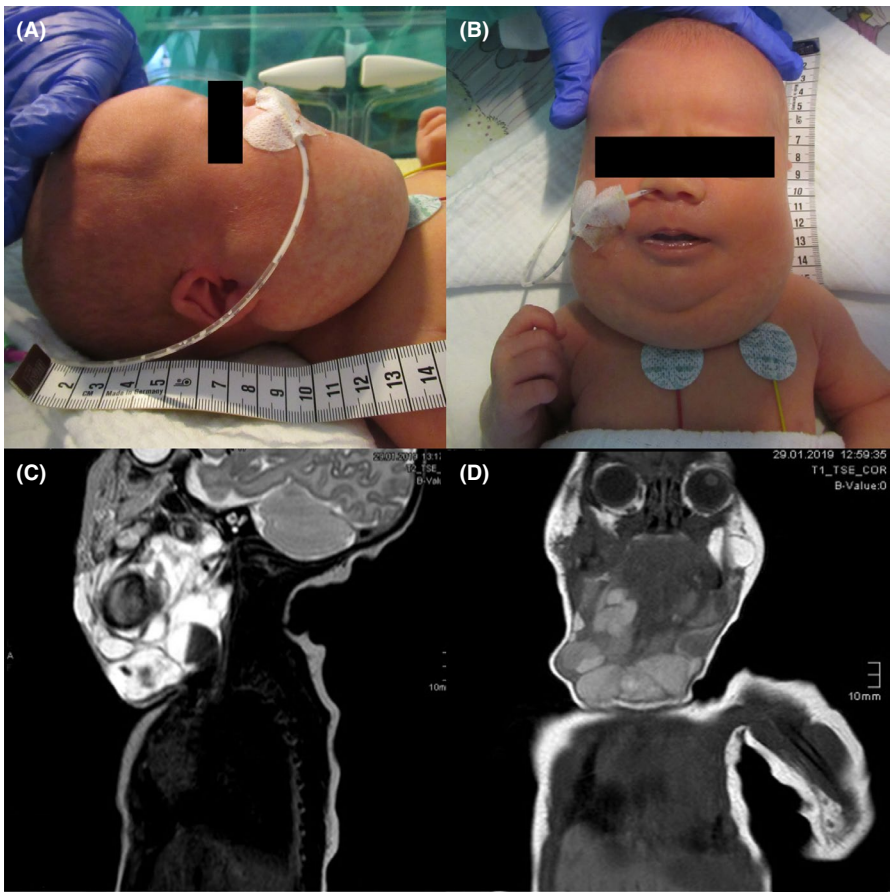

FIGURE 2 Postnatal photograph documentation: Newborn six days postpartum (A, B) and MRI seven days postpartum (C, D). (A) Side view of the face: The tumor seemed to infiltrate the base of the mouth, and the mass could not be separated from the upper thoracic aperture. (B) Frontal view of the face: The tumor extends from the right submandibular region across the front of the neck to the opposite side. (C) T2-Turbo-Spin-Echo-Sagittal: The tumor shows both hypointense, solid components and hyperintense, fluid-filled levels within the mass. (D) T1-Turbo-Spin-Echo-Coronar: The lymphangioma presents as multicystic, multiseptated, scattered structures with diffuse infiltration of its environment.

Images from the Department of Pediatrics and the Department of Radiology, University Hospital Schleswig- Holstein, Campus Lübeck

increasing frequency it has been shown that anterolateral lymphangiomas receive their growth stimuli by activating missense mutations characterizing regional-located tumors in PROS.[11,12] Axt-Fliedner et al. mentioned that theories of origin of lymphatic malformations include the failure in connection between the lymphatic and the venous system and that they could be suitable to explain the origin of lymphangiomas embryologically.[5,8] However, they also emphasized that in cases with late presenting, regional-located, and anterolateral lymphangiomas, this theory has to be questioned.[8] It therefore might be that late-presenting lymphangiomas beyond 30 weeks of pregnancy rather arise as a result of direct alteration in DNA from a postzygotic PIK3CA mutation.

Depending on the time of postzygotic cell division in embryogenesis, either somatic or, even rarer, constitutional mutations are the result.[6,9,15] As one of the most frequent missense mutation hotspot, c.1633G>A;p.Glu545Lys was identified in the helical domain of PIK3CA.[6,16] Hotspot mutations, activating, gain-of-function variants, show significantly elevated biological and biochemical activities.[14,16] These are often associated with higher numbers of transformed cell foci suggesting more rapid cell proliferation.[17]

In 2015, diagnostic criteria have been defined by Keppler-Noreuil et al. to standardize entities that originate from PIK3CA mutations and to simplify the diagnostic workup.[14] Accordingly, in the present case, the regional-located and sporadic overgrowth of predominantly lymphatic tissue of the fetal neck, already detected prenatally and classified as a lymphangioma, combined with the molecular biological detection of the somatic mutation in the PIK3CA gene with low-level mosaics clearly point to the definitive diagnosis of a disorder within the spectrum of PROS.

Due to their inexorable growth throughout all tissue layers, diagnosis and treatment of lymphangiomas within PROS disorders are often difficult.[3,4,8] However, prenatal ultrasound remains the primary diagnostic method of choice in the detection of congenital tumors. Additional volume ultrasound, combined with color Doppler interrogation, may act as an adjunct in establishing the most likely diagnosis as it potentially provides valuable information regarding the spatial relationship between surrounding cervical structures and the general extent of PROS disorders.[19] The value of an additional fetal MRI to accomplish the diagnostic workup and to give further essential information, particularly in unfavorable maternal conditions (high body mass index) and in complex fetal tumors with multiloculated masses in a variety of affected anatomical regions, has been highlighted by a number of publications.[8,19,20] Combined with information from 3D volume ultrasound, it can increase the accuracy of prenatal diagnosis including location, architecture of tissue, and volume or intracranial or thoracic spread.[18,19]

Histopathologically, in the present case, the cyst wall-coating cells presented themselves without expression of D2-40, a lymphatic endothelial marker, but showed clear CD31 expression, characterizing blood vascular endothelial cells, so that the finding was classified most likely as a cavernous hemangioma due to the complex histologic pattern (Figure 3). But considering the clinical aspects, a lymphangioma should be assumed. The D2-40 negativity does not exclude a lymphangioma. A distinct histological or immunohistochemical differentiation between a lymphangioma and a hemangioma was not possible. Due to the histological expression pattern ($CD31^+/D2\text{-}40^-$), it is most likely that endothelial cells harbor the PIK3CA mutation.[13,21]

All case reports published so far highlight the complexity of prenatal diagnosis of somatic mosaic mutations.[9,18] In 2014, Keppler-Noreuil et al. also defined testing eligibility criteria for somatic PIK3CA mutations.[17] Adequate tissue sampling is already a challenge postnatally—and, above all, as a highly invasive procedure, prenatally.[17,18] Maybe cultured amniocytes obtained by amniocentesis for prenatal diagnosis might be promising and are less invasive.[9,17,18]

Using NGS, the sensitivity of genetic testing has improved significantly and molecular diagnosis of somatic overgrowth has become feasible.[15–17] By now, mosaic levels can be detected with a variant allele frequency (VAF) down to 1%.[16] In the tissue received in this case from multiple biopsies, the activating missense mutation hotspot c.1633G>A;p.Glu545Lys with low-grade somatic mosaic and a VAF of 6.5% was detected. This is one of the most frequent mutation hotspots in the PIK3CA gene, causing somatic overgrowth in PROS. Only with the change from the pure morphologic description of lymphangiomas to the recognition of their molecular causes, they can be categorized into the spectrum of PROS diseases.

The identification of a component of the PI3K-AKT-mTOR signaling pathway can partly explain the effect of the mTOR-inhibitor Sirolimus, which resulted temporarily in a minimal size reduction. The targeted application of a PIK3-inhibitor could be more promising, even as a serious alternative treatment to surgical debulking. Finally, obtaining tissue for histopathological and molecular genetic examination to confirm the definitive diagnosis is mandatory.[18]

From a therapeutic perspective, debulking procedures are the most promising approach yet.[3–6,8,13] However, in the future, a shift from surgical debulking to personalized, targeted pharmacological intervention has been proposed.[15,18] Pharmacological therapy approaches are sclerosing therapy of fetal neck lymphangiomas with Bleomycin or Picibanil (OK-432), maybe prenatal. In addition, various molecule inhibitors, targeting different components of the PI3K-AKT-mTOR signaling pathway, are under clinical investigation: mTOR-inhibitors like Sirolimus (SRL or Rapamycin) or Everolimus (RAD-001) and recently, PIK3-inhibitors like Alpelisib (BYL719). Due to the increasing understanding of molecular biology of PROS disorders, targeted therapies are highly promising and less invasive. Moreover, it can improve quality of life of affected patients.[2,4–6,10,13,22]

Despite all efforts, there is a high risk of recurrence.[4,10] Fetal prognosis of congenital tumors of the neck depends largely on the nature of lesion, on their location and size, on the affected surrounding structures, and on the presence of other anomalies.[7,20]

4 | CONCLUSION

PIK3CA-related overgrowth spectrum encompasses rare genetic disorders resulting from somatic, mosaic gain-of-function mutation of the PIK3CA gene. As a result of the genetic mosaicism, the clinical presentation is extremely variable. Comprehensive diagnostics are expensive and time-consuming, and they place an unnecessary burden on the infant and its family. A prenatal diagnosis of this extremely rare mutation enables physicians a simplified interdisciplinary perinatal management. Moreover, it offers parents and family members to be involved in the assessment process

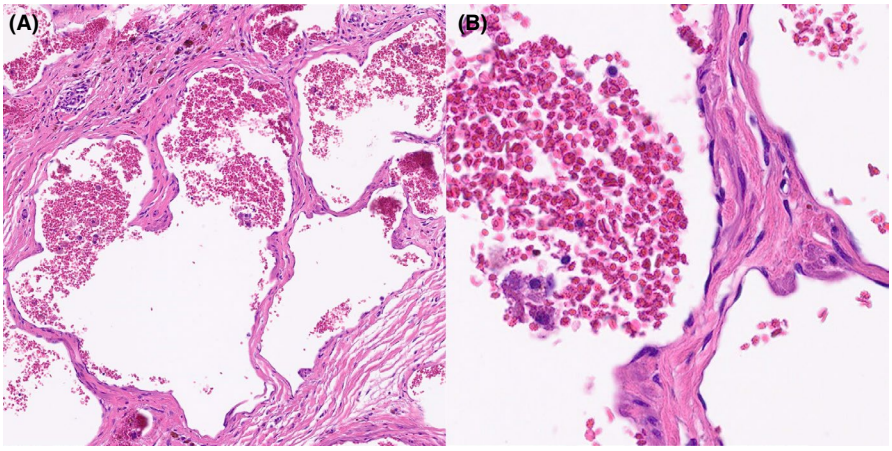

FIGURE 3 Representative histopathological images (hematoxylin/eosin, HE) showing complex vessel structures lined by unsuspicious endothelial cells. (A) 10× magnification. (B) 40× magnification.

Images from the Institute of Pathology, University Hospital Schleswig-Holstein, Campus Lübec

in the context of informed consent. Nevertheless, diagnosis of PROS remains challenging, both pre- and postnatally and unfortunately, the diagnosis is rarely made prenatally. Therefore, physicians and parents stay in the dark for a long time regarding a definitive diagnosis and promising therapy.

ACKNOWLEDGMENTS

Thanks to everyone involved, for their constructive cooperation and support on this article. Published with written consent of the patient.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission. JLS: contributed to case analysis, literature review, and manuscript writing and editing; JW: contributed to case analysis, literature review, diagnosis of the patient and patient care, and manuscript editing; MG: contributed to case analysis, diagnosis of the patient and patient care, and manuscript editing; CD: contributed to manuscript editing; YH, AO, GS, KT-L, and LT: contributed to diagnosis of the patient and patient care.

ETHICAL APPROVAL

This article does not contain any studies with human participants performed by any of the authors. The written informed consent of the patient was given.

INFORMED CONSENT

Informed consent was obtained from the patient for publication of this case report.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Scharf JL, Gembicki M, Dracopoulos C, et al. Lymphangioma of the fetal neck within the PIK3CA-related-overgrowth spectrum (PROS): A case report. *Clin Case Rep*. 2021;9:e04527. https://doi.org/10.1002/ccr3.4527