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The First Familiar Case of PTEN-Related Disorder Reported in Albania

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PTEN hamartoma tumor syndromes (PHTS) are a group of genetic disorders inherited in an autosomal dominant manner and linked to the germ line of the tumor suppressor gene *PTEN* located on 10q23 (OMIM 601728).[1-4] The PHTS, characterized by a broad, extremely variable, and often overlapping spectrum of clinical features, comprises different disorders such as Cowden syndrome (CS, OMIM 158350), Bannayan-Riley-Ruvalcaba syndrome (BRRS, OMIM 153480), *PTEN*-related Proteus syndrome (OMIM 176920), and *PTEN*-related Proteus-like syndrome.[1-4] The *PTEN* germline mutations have also been described in ~10%-20% of those with macrocephaly and autism spectrum disorder (ASD), as well as in a few cases of megalencephaly and hemimegalencephaly, and VATER syndrome (vertebral abnormalities, anal atresia, tracheoesophageal fistula with esophageal atresia, and radial or renal dysplasia).[1-3,5]

We are describing a case of a 3-year-old child who came to the hospital as her parents complained mostly about the severe pain their daughter manifested when walking. Physical examination showed a swelling of the right lateral knee, right thigh, and calf, limited painful joint movement, and numerous fibroblastic lesions on the trunk and limbs. According to the parent, the skin's elements have been present since the child was two and a half years old and have been getting bigger and more numerous over time. They range in size from 5 to 6 cm in diameter, were rounded or oval, not hyperpigmented, deeply infiltrated, and few of them were painful during the palpation. Interestingly, the parents were not concerned about their presence, as her father has the same generalized lipomas. Macrocephaly (>2 SD), hypotonia, and scoliosis were among the most noticeable physical findings. Ultrasound examination of soft tissues showed the presence of solid hyperechoic intramuscular lesions of about 6×1.8 cm in the right gluteal muscles, between the right vastus lateralis muscles, and the tensor fasciae latae as well in the right gastrocnemius muscle with well-defined margins and presence of vascularization on Doppler, with features more consistent with hemangiomas or hamartomas. Magnetic resonance imaging revealed an excessive amount of intra-abdominal adipose tissue (yellow arrows), an aspect of peritoneal lipomatosis as well as a presacral heterogeneous lesion (red arrows) in the T1FS, T2 sequences (red arrows). In addition, a solid heterogeneous lesion on T2 and T1 at the level of the right gluteus muscles (blue arrows) and on the left gluteus maximus muscle (green arrows) (Figure 1). The lesions significantly enhance after the injection of intravenous contrast (Gadolinium). The biopsy of one of the lipomatous lesions was performed, and the histopathology report indicated fibro lipoma. When the patient's parents and brother were examined, it was found that her father had generalized lipomas, while her mother and brother were both normal.

The main complaint of our patient's parents was the severe pain that their daughter had while walking. However, a generalized lipomatosis found as an incidental finding by careful physical examination, as well as the presence of the hamartoma of soft tissue, macrocephaly, and hypotonia, guided us to *PTEN* gene testing.[1-4,6,7] Molecular genetic testing in our patient identified the presence of a heterozygous, pathogenic variant c. 635-1G>C, which is predicted to disrupt the highly conserved acceptor splice site. This variant was detected in her father in a heterozygous state and is absent in the patient`s brother, confirming the *PTEN*-related diagnosis in our patient and her father which, to the best of our knowledge, is

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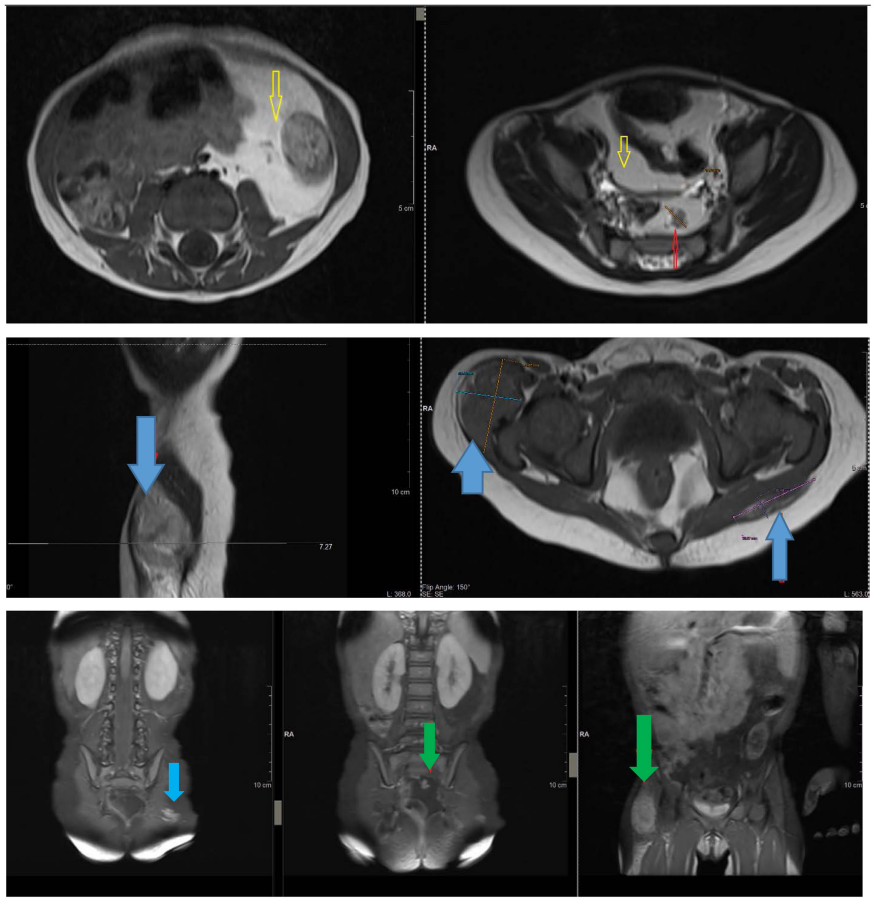

Figure 1. Magnetic resonance imaging revealed an excessive amount of intra-abdominal adipose tissue (yellow arrows), an aspect of peritoneal lipomatosis as well as a presacral heterogeneous lesion (red arrows) in the T1FS, T2 sequences (red arrows). A solid heterogeneous lesion on T2 and T1 at the level of the right gluteus muscles (blue arrows) and on the left gluteus maximus muscle (green arrows).

the first familial case with this syndrome described in Albania. We want to draw attention to the fact that to identify patients for *PTEN* mutation testing in pediatric patients it is important to be aware of the updated diagnostic criteria for PHTS as well as to conduct a meticulous physical examination and obtain a thorough familial history. Since PHTS is a hereditary syndrome, the finding of a germline *PTEN* mutation in our patient helped to detect the same mutation in her father, who was not previously suspected of having the same syndrome despite having several lipomas.[3-4,6,8,9] The pathogenic variant found in our patient has previously been described as disease-causing for Cowden disease (CD). Since some clinical characteristics of CD and BRRS have been observed in people within the same family with the same *PTEN* variant, CS and BRRS are thought to be the same disorder with variable expression and age-related penetrance typical of tumor suppressor disorders. For these reasons, it has been suggested that it is not helpful to classify *PTEN*-related disorders into separate clinical syndromes.[1-4,6,10] In addition to the higher risk of early onset, bilateral, and multifocal cancer that is typical of hereditary cancer syndromes, PTHS patients also have an increased risk of breast, thyroid, kidney, endometrial, colon, and melanoma cancers, according to several publications.[1-4,6,11] We emphasize that our patient and her father will be carefully monitored for cancer and specific gastrointestinal and vascular complications following the cancer surveillance strategy and appropriate guidelines.[1-4,12-14] As some PHTS patients also experience neurodevelopmental and cognitive issues like ASD and developmental delays, our patients will be regularly followed up by the respective specialists.[4,15] We would like to point out that besides the treatment of her actual complaints, we will continuously follow this patient and her father following the interdisciplinary surveillance program (which also includes parental education) prepared by a multidisciplinary team. In addition, the present case demonstrates how identifying genes linked to a disorder may help in early identification, enabling the right diagnosis, treatment, and follow-up, as well as helping patients to receive the most effective medical care.

Informed Consent: Written informed consent was obtained from the patient's parents who agreed to take part in the study.

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