Immature Teratoma in an Adolescent with Proteus Syndrome; A Novel Association.

John Underwood[1], Christopher Ours[2], R. Burns[1], and Michael Ferguson[1]

[1]Indiana University School of Medicine
[2]National Institutes of Health

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Abstract

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TITLE

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John S. Underwood[1], Christopher Ours[2], R Cartland Burns[3], Michael J Ferguson[4]

[1]Indiana University School of Medicine, Departments of Internal Medicine and Pediatrics

[2]National Human Genome Research Institute, National Institutes of Health

[3]Indiana University School of Medicine, Department of Surgery

[4]Indiana University School of Medicine, Department of Pediatrics

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ABSTRACT

Proteus syndrome (PS) is a complex disorder characterized by variable clinical findings of overgrowth and tumor susceptibility. This report presents the first known association between PS and an ovarian germ cell tumor in an adolescent with immature teratoma. A review of the diagnosis of PS and associated tumors is included.

KEY WORDS

Proteus syndrome, immature teratoma, abdominal mass, tumor, adolescent

PATIENT HISTORY

Our patient is a seventeen-year-old female with previously established diagnosis of Proteus syndrome (PS). Her medical history is notable for neuronal migration disorder, spastic quadriplegic cerebral palsy, intellectual disability, seizures, vision impairment, scoliosis with subsequent restrictive lung disease, leg-length discrepancy, and hepatic steatosis. She has a history of multiple tumors and overgrowths, briefly summarized as follows: multiple osteomas and cholesteatomas of both ear canals requiring debridement and reconstruction; gingival hypertrophy with biopsy-proven fibrous hyperplasia; jaw bone overgrowth requiring partial

resection; abdominal lipoma; and epidermal nevus of the anterior neck. Biological mother and brother are healthy, paternal history is limited, and there is no known history of consanguinity. Using the dyadic genotype-phenotype criteria from Sapp, et al. (2019) (Sapp, Buser, Burton-Akright, Keppler-Noreuil, & Biesecker, 2019) she meets clinical-molecular diagnostic criteria for PS given bony overgrowth (5 points), dysregulated adipose tissue/lipoma (2 points), linear verrucous epidermal nevi (2 points), vascular malformation (2 points), facial phenotype (2 points) for a total score of 13 as well as a previously identified *AKT1* c.49G>A (p.E17K) variant from a skin biopsy of affected tissue and would receive an additional 5 points for*asymmetric overgrowth or cystic changes of specific organs* due to polycystic left ovary, discussed in addition to a previously identified hemimegalencephaly, for a total score of 18. Given her score was [?] 10, our patient met criteria for a clinical-molecular diagnosis of PS.

CASE PRESENTATION

Our patient presented to the emergency room for acute on chronic abdominal pain following a one-month period of weight gain and progressive abdominal distension and discomfort. In recent weeks, she had low-grade fevers treated unsuccessfully with a one-week course of cefdinir. At presentation, her review of systems was positive for fevers, fatigue, cough, and abdominal pain. She had no nausea or vomiting and was voiding and stooling normally. She was afebrile. On exam she was in no acute distress, but her abdomen was distended and diffusely tender with a large mass appreciated best in the right upper and lower quadrants. Dysmorphic features included frontal bossing, protuberant jaw with limited mobility, depressed nasal bridge, and macrocephaly. Eye exam was notable for bilateral exotropia and nystagmus. On neurologic exam she had low tone with normal strength, and she grunted or clapped to express her needs and could occasionally follow simple commands. Musculoskeletal exam was notable for severe thoracolumbar scoliosis.

CT of the abdomen and pelvis revealed a 35 x 23 x 16 cm mass in the abdomen and pelvis with large cystic components, fat, calcification, and soft tissue attenuation, which was highly suggestive of a large ovarian teratoma (Figure 1A, Figure 1B). Marked mass effect on surrounding organs of the abdomen and pelvis was noted as well. CBC and CMP were unremarkable, including a normal bilirubin, AST, ALT, LDH, alkaline phosphatase AFP, and β-hCG were also normal. A serum CA125 was elevated at 100.2 units/mL (normal < 35.0 units/mL). A urinalysis was unremarkable. COVID testing was not performed as this encounter took place before the coronavirus pandemic.

She had an exploratory laparotomy and was found to have to large ovarian masses requiring bilateral oophorectomy (Figure 2). The right ovarian mass measured 36 x 26 x 13 cm and weighed 6,520 gm. Intraoperatively, the capsule appeared intact with no peritoneal implants and was considered a complete resection with no identified enlarged lymph nodes. No peritoneal washings were obtained. The left ovarian mass measured 14 x 11 x 5 cm and weighed 380 mg. The patient tolerated the procedure well and had an unremarkable post-operative course, during which she was placed on prophylactic enoxaparin given the increased risk of venous thromboembolism in Proteus syndrome (Keppler-Noreuil et al., 2019). She was discharged after four days and evaluated one month later in oncology clinic, where repeat CT abdomen/pelvis showed no residual disease. Final pathology of the right ovarian mass indicated Grade III immature teratoma based on the extent of primitive neuroepithelial elements (Figures 3A-C). Due to complete resection, she was considered stage I, per Children's Oncology Group (COG) staging, and stage IA by the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) classification (Prat, 2014). Final pathology of the left ovarian mass revealed polycystic ovary.

DISCUSSION

Proteus syndrome is an uncommon and complex disorder characterized by variable clinical findings of overgrowth and tumor susceptibility. It was first described by Cohen and Hayden in 1979 (Cohen & Hayden, 1979) and later termed Proteus syndrome by Wiedemann et al in 1983 (Wiedemann et al., 1983) due to its phenotypic heterogeneity. Correct diagnosis is paramount in PS and can be difficult due to the diversity of presentations (L. Biesecker, 2006; L. G. Biesecker, 2001). Since the publication of a revised diagnostic criteria in 2006 (L. Biesecker, 2006), an activating mutation in *AKT1* c.49G>A p.E17K of the PI3K-AKT pathway

has been associated with PS (Carpten et al., 2007; Lindhurst et al., 2011). In order to include genotype in the diagnostic criteria a dyadic genotype-phenotype approach has been proposed (Sapp et al., 2019). Our patient meets genotype and phenotype diagnostic criteria, as described previously. In a 2004 review of 205 reported cases of PS, less than half of published cases of PS (47%) met diagnostic criteria, and importantly reported cases in this study that met the PS criteria had a higher incidence of morbidity and mortality compared to those in the non-Proteus group (Turner, Cohen, & Biesecker, 2004). The need for molecular testing is further highlighted by phenotypic overlap with similar but distinct syndromes such as PTEN hamartoma tumor syndrome and PIK3CA related overgrowth spectrum (PROS) (Barker et al., 2001; Caux et al., 2007; Cohen, Turner, & Biesecker, 2003; Smith et al., 2002; X. Zhou et al., 2001; X. P. Zhou et al., 2000).

Tumors usually associated with PS have been reviewed elsewhere (L. Biesecker, 2006; L. G. Biesecker et al., 1999; Gordon, Wilroy, Lasater, & Cohen, 1995; Turner et al., 2004) and include cerebriform connective tissue nevi, bilateral ovarian cystadenomas, parotid gland monomorphic adenomas, lipomas, regional lipohypoplasia, and vascular malformations, all of which are considered in the diagnostic criteria (Cohen, 2014; Nelson & Ruben, 2008). In regards to an association with germ cell tumors, Hong et al. (2010) (Hong et al., 2010) described a girl with PS found to have a pelvic mass at 21 months of age that was later resected at 5 years of age and found to be a mature cystic teratoma of the left ovary. Another case report by Zacharious and Krug, et al (1996) (Zachariou, Krug, Benz, & Daum, 1996) described a young boy with PS and a mature sacrococcygeal teratoma, however a panel of experts later reviewed this case, among others, and determined that this patient did not meet diagnostic criteria for PS and likely had a non-Proteus condition (Turner et al., 2004). Our case describes an adolescent female with PS who developed a massive immature teratoma, which represents an association between PS and an ovarian germ cell tumor not previously described in PS.

Recommendations from Children's Oncology Group (Billmire et al., 2014) and the National Comprehensive Cancer Network (Network, 2020) support surgery-only in stage I patient with periodic surveillance thereafter. There has been debate between adult and pediatric providers regarding the value of chemotherapy should this tumor relapse. Given the activating AKT1 mutations found in PS, there are reports of AKT1 variants in testicular germ cell tumors (GCT) (Feldman et al., 2014), but not ovarian GCT. Though not AKT1 activating mutations, similar pathway proteins, PIK3CA and PTEN, have shown mutations in ovarian GCTs and AKT1 amplification was additionally noted (Van Nieuwenhuysen et al., 2018). Additionally, there is a recent case report in Proteus syndrome with different ovarian tumor pathology, low grade serous ovarian carcinoma, that showed response to the AKT inhibitor, miransertib (Leoni et al., 2019). These findings collectively argue that treatment with an AKT inhibitor should be explored in ovarian immature teratomas, especially ones associated with Proteus syndrome.

In summary, we report the first known association with PS and development of an immature teratoma. Given the germline AKT1 variant in this case and the lack of chemotherapy response usually observed in pediatric immature teratomas, treatment with an inhibitor of PI3K-AKT-MTOR pathway makes an intriguing option should recurrence occur.

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