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Unusual presentation of Loeys-Dietz syndrome; a case report of clinical findings and treatment challenges

A multidisciplinary approach.

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Abstract

BACKGROUND

Loeys-Dietz syndrome (LDS) is a rare autosomal dominant syndrome characterized by heterozygous mutations causing multisystemic alterations. It was recently described in 2005 and today, we have identified at least six different subtypes. Classically presenting with aortic root enlargement or aneurysms and craniofacial and skeletal abnormalities, with specific arterial tortuosity at any site. The differential diagnosis of LDS includes atypical Marfan syndrome, vascular Ehlers-Danlos syndrome, Shprintzen-Goldberg craniosynostosis, and familial aortic aneurysm and dissection syndrome.

CASE SUMMARY

We present a case study of a 35 year-old female that came into the emergency department because of lower gastrointestinal bleeding and severe abdominal pain. The Computed Tomography revealed vascular tortuosity in almost every abdominal vein.

CONCLUSION

This case report will help us analyze the infrequent presentation of LDS type 4 and the numerous complications that it implies, underlying the importance of publishing more cases in order to expand our knowledge and offer better treatment for these patients. Differential diagnosis, clinical presentation and treatment options for this syndrome are discussed in this article.

Key Words: Loeys-Dietz syndrome; pulmonary embolism; gastrointestinal bleeding; rare genetic disease; therapeutic angiography; unusual presentation; rare disease; case report.

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Core Tip: Diagnosing and treating Loeys-Dietz syndrome within its many comorbidities is very challenging for most clinicians. The suspicion of this disease in a patient without aortic aneurysm should not be discarded. We describe a clinical case to enhance the clinical suspicion of this genetic disease for a proper management within a variety of medical specialties. The management and follow up depends upon each patient and their manifestations.

INTRODUCTION

Loeys-Dietz syndrome (LDS) is an autosomal dominant syndrome characterized by heterozygous mutations in the genes transforming growth factor β receptor (TGFBR1 or TGFBR2) and other related genes such as SMAD2, SMAD3 (Small Mothers Against Decapentaplegic), TGFB2, and TGFB3, which modify the physiological development and function of the extracellular matrix, resulting in cardiovascular and multisystem abnormalities (1,2) It´s clinical classic manifestation consists of bifid uvula and/or cleft palate, hypertelorism, and tortuous aortic and arterial aneurysms (3). Although these were the most typical characteristics when it was first described in 2005, a wide range involvement of many different organ systems was also observed due to its variable clinical expression.

In the first descriptions of this syndrome, LDS patients were secerned into two categories, according to craniofacial or cutaneous traits. Nonetheless, these findings are now believed to be part of a spectrum within the LDS syndrome (4).

The greater number of individuals with LDS 1 and 2 show vascular features compelling critical aortic dissection and large aortic aneurysms, thus early death has been reported at a median of 37 years (4). LDS type 4 syndrome has been scarcely reported, therefore its clinical presentation is not flawlessly known yet. It is puzzling that deletions and loss-of-function mutations of TGFB2 induce an increased activity of TGF-β (6). Some dermatologic features as easy bruising, velvety and translucent skin and atrophic scaring, are additionally reported at irregular degree (Table 1).

The diagnosis of Loeys-Dietz syndrome is established in a person without a known family history of LDS who has a heterozygous pathogenic variant in SMAD2, SMAD3, TGFB2, TGFB3, TGFBR1, or TGFBR2 and EITHER of the following: (7)

- Aortic root enlargement (defined as an aortic root z-score ≥2.0) or type A dissection
- Compatible systemic features including characteristic craniofacial, skeletal, cutaneous, and/or vascular manifestations found in combination. Additional emphasis is given to arterial tortuosity, prominently including the head and neck vessels, and to aneurysms or dissections involving medium-to-large muscular arteries throughout the arterial tree.

Some of the alterations described include skeletal, craniofacial, cutaneous and ocular alterations. Whilst LDS shows clinical overlap with Marfan syndrome (MFS), it can be clinically distinguished from the latter. Some clinical manifestations that can be found in both LDS and Marfan syndrome involve pectus deformities, aortic root aneurysm, arachnodactyly and scoliosis. Discriminating features in LDS are micrognathia, cranial alterations, hypertelorism, cleft palate or bifid uvula, intervertebral disc degeneration, club feet, and primarily dilatated and tortuous arteries and early aortic rupture (Table 1). In LDS there aren't the typical marfanoid habitus and the lens displacement.

Histologic analysis of the original series reported diminished elastin content and chaotic elastic fibers in the aortic media of patients with classic Marfan Syndrome (MFS) or mutations in TGFBR2 compared with samples from age-matched controls (2). Morphologic analysis revealed loss of intimate spatial association between elastin deposits and vascular smooth muscle cells. These features were noted in young children and in the absence of inflammation, expressing a dire imperfection in elastogenesis alternatively to secondary elastic fiber elimination. Furthermore, a noticeable overabundance of aortic wall collagen in individuals with MFS compared with age-matched controls was highlighted in individuals with TGFBR2 mutations. As multiple collagens normally expressed in the aorta are derived from early-induced TGF-β target genes (including COL1A1 and COL3A1), this information consists with increased (rather than decreased) TGF-β signaling.

The differential diagnosis of LDS includes atypical Marfan syndrome, Shprintzen-Goldberg craniosynostosis, vascular Ehlers-Danlos syndrome, and familial aortic aneurysm and dissection syndrome. Arterial tortuosity syndrome is a closely related syndrome that is also characterized by severe tortuosities, stenosis, and aneurysms of large and mid-sized arteries.

CASE PRESENTATION

Chief complaints

We present a 35 year-old Hispanic woman that came into de emergency department of a private hospital in Mexico City because of lower gastrointestinal bleeding and abdominal pain. She referred that she had been having severe abdominal pain localized in the hypogastrium that was accompanied by diarrhea with clots and hematochezia for the last 48 h that wasn't relieved by over the counter medications.

History of present illness

Recent prescription for hormonal contraceptives.

History of past illness

Her past medical history revealed prior lower GI bleedings during childhood that resolved spontaneously, hypothyroidism and a recent diagnosis for polycystic ovary syndrome that required her to take hormonal contraceptives for five months prior to her visit.

Personal and family history

Mother with diabetes mellitus type 2.

Physical examination

At physical examination she was tachycardic (112 beats per minute) with normal blood pressure (112/75 mmHg) and 90% oxygen saturation. She hadn't had fever or cough. She had sinus tachycardia with a clear systolic heart murmur and diffuse severe abdominal pain. She also referred upper back pain consistent with muscular contracture. The rest of the physical examination was normal.

Laboratory examinations

The only abnormal findings in her laboratory test were low albumin (3.1) an elevated D dimer at 10,000 µg/mL (normal value: less than 0.5 µg/mL). We ordered laboratory tests to search for hematologic disturbances and thrombophilias such as factor V Leyden, homocistein, lupic anticoagulant, antineutrophil cytoplasmic antibodies (ANCAs), extractable nuclear antigen (ENA) panel (ENAs), rheumatoid factor, anticardiolipin antibody, all which eventually came out completely normal.

Imaging examinations

Our team of gastroeneterolgists performed an upper endoscopy and colonoscopy to search for the etiology of her lower GI bleeding. The colonoscopy revealed tortuous internal hemorrhoid veins and an increased caliber in the colon´s vessels as well as in terminal ileum (Figure 1), which increased suspicion for an ongoing venous thrombosis *vs* mesmeric ischemia. Biopsies were taken.

The thoracoabdominal Computed Tomography scan with IV contrast revealed segmental pulmonary thromboembolism with bilateral pulmonary infarctions as well as abnormal vessel distribution around the abdomen consistent of tortuous and bizarre vessels (Figure 2). There was portal vein atresia with no hepatic arteries easily found. We found a venous shunt from the left mesenteric vein to the right colonic vein and we observed significant varicose dilatation of the inferior mesenteric vein and confluent branches of the splenic vein, congestive conflicting veins of the superior mesenteric system, as well as engorgement of the inferior vena cava, renal veins, common iliac veins and internal right iliac vein. She was admitted to the intensive care unit for treatment.

We ordered an echocardiogram that showed preserved ejection fraction with increase pulmonary venous pressure estimated in 62 mmhg. We started her on enoxaparin (1 mg/kg) to treat her pulmonary embolism at therapeutic doses. During the first 48 h of admission, she developed grade three anemia (hemoglobin 8.7) and continued bleeding even more through her lower gastrointestinal tract, worsening her tachycardia. She needed blood transfusions and we were forced to hold her anticoagulation for around 72 h to prevent her from massive bleeding. We started oral iron at this time.

We immediately programed her for an angiography procedure to stop her anomalous vessels from bleeding into her colon. Embolization of her left mesenteric vein and her right colon vein immediately stopped her from bleeding.

MULTIDISCIPLINARY EXPERT CONSULTATION

Because of the severe abdominal pain that persisted despite of multiple pain killers including opioids, she wasn't able to feed herself, so we decided to give her total parenteral nutrition.

At 72 h after suspending anticoagulation she developed sudden dyspnea, her oxygen saturation dropped to 76% and her heart beats sped up to 145 beats per minute. Her blood pressure was dropping to 80/60 mmHg. Because of the high suspicion of a new pulmonary embolism, a thoracic CT scan was made showing a complete obstruction of the right pulmonary vein (Figure 3) that needed thrombolysis and thrombectomy which was immediately done. During this procedure she needed several blood transfusions and an inferior vena cava filter was inserted. At this point we started a heparin infusion in order to control her anticoagulation. Later on, she continued with transvaginal bleeding, not corresponding to her period, signaling that there was more pressure on other venous shunts that we had not seen in the previous angiography. A second angiography found at least three more aneurysmatic lesions in the splenic artery (Figure 4) which required

more coiling, achieving a successful control of her bleeding. More blood transfusions were needed at this time.

FINAL DIAGNOSIS

We also ordered genetic tests to confirm our suspicion of a collagen related genetic disorder. A whole exome sequence (WES) and copy number variation was requested. The results showed heterozygous missense mutation in TGFB2 gene, variant c.439C>T p.(Prol47Ser) in Exon 3, categorized as uncertain significance mutation consistent of Loeyz-Dietz syndrome type 4. After eleven days of hospitalization, we eventually were able to discharge her and continue management at home.

TREATMENT

After resolving her anatomic abnormalities, the main treatment was anticoagulation.

OUTCOME AND FOLLOW-UP

After eleven days of hospitalization, we eventually were able to discharge her and continue management at home. She has been taking her anticoagulation to stop her for developing new embolic event and her follow up visits are every six months with complete blood count to search for signs of bleeding. Colonoscopy and transthoracic echocardiogram are taken every year.

DISCUSSION

The abnormal presentation of this genetic syndrome during adulthood is very bizarre. Most of previous reports of LDS type 4 have described clinical presentation during childhood, which almost always debuted with aortic aneurysm and some mental retardation, not the case with this patient. Few reports have described a late presentation of LDS with aortic aneurysm (8), nevertheless, our patient debuted at 35 years-old, when the actual life expectancy has been estimated at thirty seven.

LDS is a bizarre autosomal dominant disorder with extensive widespread implications. The recently proposed nosology states that a mutation in any of the formerly described four genes added to a documented arterial/venous aneurysms or dissection should be considered as diagnostic for LDS. Consequently, with our case report we described sporadic signs of LDS4 that need to be considered within LDS spectrum even in the absence of aortic aneurysm.

TGFB2 has a universally evidenced role in chondrocyte maturation and endochondral ossification as it is expressed by chondrocytes during a late stage of hypertrophic differentiation (10). It participates in bone remodeling, modulating both bone deposition and turnover (11), contributes to the survival of the osteoblasts (12), interacts with collagen (13), and enhances bone formation and cortical development (14). There have been reports describing a remarkable association between the low expression of TGFB2 and hip dysplasia (15).

The data indicate that the TGF-β latency profile in chondrocytes undergoing maturation and endochondral ossification is convoluted, a reflection of the potency of this factor and the pleiotropic effects evoked by it. Therefore, there is a need for multiple regulatory levels to control TGF-b activity (10).

Reports from previous case series with LDS show that approximately 55% to 60% of patients have aneurysmal disease beyond the ascending aorta, and both report late mortality of 9% and 14% (16). Our patient´s anatomical abnormalities including portal atresia conducted us at first to search for other genetical causes including Abernathy syndrome, characterized by diversion of portal blood away from the liver. There is either an absence of portal vein, type I congenital extrahepatic portosystemic shunt or presence of thin portal vein radicles (congenital extrahepatic portosystemic shunt, although it never really described her whole anatomic alterations. Our patient had mild typical fascies and no joint laxity.

The main clinical challenge with this patient was to control her massive gastrointestinal and vaginal bleeding caused by abnormal tortuous veins while treating her pulmonary embolism and preventing a new one with anticoagulant therapy. Also, with that many

blood transfusions required, the tissue sample for the genetic test had to be taken from the saliva and sent to Germany for further analysis. When the diagnosis of LDS is made, it is critical to search for further typical or atypical features like cerebral aneurysms or venous tortuosity that could compromise the person´s life. Furthermore, it is important to consider optimal treatment with calcium and vitamin given the skeletal fragility and low bone mass seen in LDS as in other connective tissue diseases (17). Many different aspects including a variety of specialists have to be considered in order to make valuable recommendations to these patients including cardiological, gastrointestinal, hematological, oncological and orthopedical guidance. The follow up visits of our patient included anticoagulant monitorization, annual colonoscopy and echocardiogram.

CONCLUSION

Fundamentally, prudence must be taken with regard to recommendations for patients with LDS syndrome. Moreover, it is plausible that the former LDS reports have immersed in the most severe features of the disorder, giving the unreal conclusion of a life-threatening natural history (16), although this may not be the case in every patient.

As diagnostic methods have improved and the LDS syndrome spectrum is more recognized, we have been identifying phenotypically less severe forms and treating them much earlier in their clinical spectrum. These reports provide additional understanding of the behavior of this disorder among the medical community, and as we continue to treat and study patients with LDS, this knowledge will undoubtedly continue to evolve resulting in further improved outcomes and lengthen life expectancy. The more case reports about this syndrome are published, our medical knowledge about the wide clinical features expands and we become more experienced providing these patients better counseling to improve their life quality and reduce their mortality.

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6	Paolo Fontana, Rita Genesio, Alberto Casertano, Gerarda Cappuccio et al. "Loeys–Dietz syndrome type 4, caused by chromothripsis, involving the TGFB2 gene", Gene, 2014 Crossref	35 words — 1%

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