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Bilateral, Full-thickness Macular Holes While Undergoing Chemotherapy

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Bilateral, Full-thickness Macular Holes While Undergoing Chemotherapy

Abstract

Background: Bilateral, full-thickness macular holes are a rare condition that can substantially affect quality of life. Macular hole diagnosis and treatment is key for these patients.

Case Report: A 71 year old Caucasian male presented with a chief complaint of distance blur in both eyes, worsening over the past 1-2 weeks. He had no diagnosis of diabetes. He added that his prostate cancer had spread and that his last treatment ended 9 days ago. He was ultimately diagnosed with bilateral, full-thickness macular holes. Referral to a retinal specialist for surgical management yielded good results.

Conclusion: This is the first case report documenting bilateral macular holes in a patient with these systemic meds to date. More research on any potential ocular side effects of these medications is recommended.

Keywords

macular hole, prostate cancer, chemotherapy

INTRODUCTION

Full-thickness macular holes can quickly impact a patient's daily life due to their effect on central vision. Blurred vision, metamorphopsia, or a central scotoma are common presenting symptoms. The prevalence of full-thickness macular holes is approximately 3:1000, with 70% of patients being female.[1,2] The age of onset for both males and females is most common in the 7th to 8th decade.[1] Full-thickness macular holes are most commonly caused by vitreous-mediated anteroposterior or tangential forces on the retinal surface.[2] A full-thickness hole interrupts all neural retinal layers from the internal limiting membrane to the retinal pigment epithelium.[3]

Classification of macular holes is useful for surgical management and prognosis. In 2013, the International Vitreomacular Traction Study (IVTS) Group developed an Optical Coherence Tomography (OCT)-based anatomic classification system for disease of the vitreomacular interface.[2] The IVTS system is presented in Table 1. This new system is based on the minimum hole width.[2] The aperture size is measured using the caliper function on spectral-domain OCT devices.[2] The minimum hole width is measured at the narrowest hole point in the mid retina.[2]

Clinical Stages	**Attributes**	**Comments**
Vitreomacular Adhesion	Vitreous adhesion to central macula with no demonstrable retinal morphologic changes	Has been called stage 0 in the past when the contralateral eye has a FTMH; normal appearance on clinical examination; no symptoms
Vitreomacular Traction	Vitreous adhesion to central macula with demonstrable changes by OCT but no full thickness tissue dehiscence; may include the following: tissue cavitation, cystoid changes in the macula, loss of foveal contour,	May or may not have yellow changes in central macula on examination; can be referred to as impending macular hole if there is a FTMH in the contralateral eye

	elevation of the fovea above RPE	
Small Full-Thickness Macular Hole	Hole ≤250 μm, may be round or have a flap adherent to the vitreous; operculum may or may not be present	Visual acuity may be relatively good; optimal size for successful repair by pharmacologic vitreolysis; very high probability of success with vitrectomy surgery
Medium Full-Thickness Macular Hole	Hole >250 but ≤400 μm; may be round or have a flap adherent to the vitreous; operculum may or may not be present	High probability of success with vitrectomy surgery
Large Full-Thickness Macular Hole	Hole >400 μm; vitreous more likely to be fully separated from the macula	Slightly less probability of successful closure with vitrectomy surgery

Table 1: Clinical Stages of the International Vitreomacular Traction Study Classification System for Vitreomacular Adhesion, Traction, and Macular Hole.[2] FTMH = full-thickness macular hole; RPE= retinal pigment epithelium

The occurrence of bilateral, simultaneous, full-thickness macular holes is rare. The risk of fellow eye involvement at 5 years is approximately 10% and the mean interval time between onset of the first full-thickness macular hole to the onset of a macular hole in the fellow eye is 26.1 months.[1,3] We report a unique case of bilateral, simultaneous full-thickness macular holes in a male while undergoing metastatic prostate cancer treatment. Given the bilateral presentation, it was necessary to further investigate for an underlying cause.

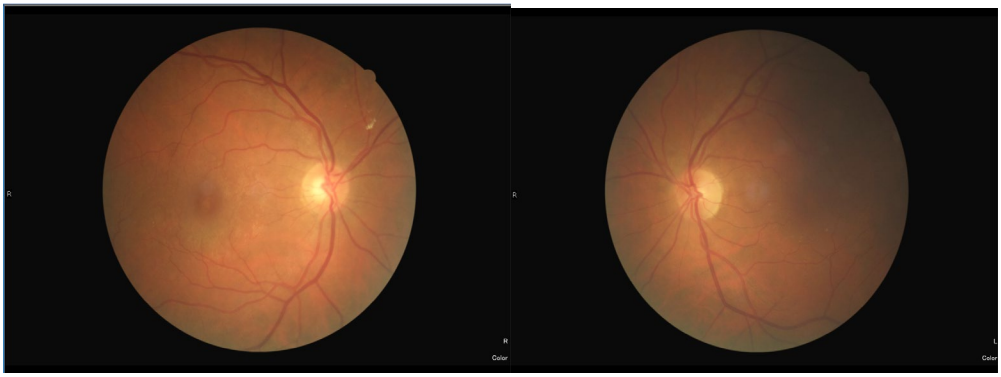
CASE REPORT

A 71-year-old white male presented with blurred distance vision in both eyes of two weeks duration. He noted difficulty reading street signs while driving and written text on television. He was being monitored bi-annually for glaucoma suspicion due to optic nerve asymmetry and had a remote history of welder's flash in both eyes. The patient's ocular history was otherwise unremarkable. Three years prior to presentation he was diagnosed with prostate cancer and eight weeks prior to his visit to the eye clinic he was diagnosed with metastatic lesions to his spine. For his metastatic disease he had undergone 5 radiation sessions, with the last treatment being 9 days prior to his initial eye examination. He began oral therapy with enzalutamide 40 mg capsules, taking 4 capsules by mouth every 24 hours.

After 4 weeks of this regimen, the patient was also given an injection of leuprolide acetate suspension (Eligard®). At week 6, he was referred to the eye clinic due to blurred vision of one week duration. With the recent addition of two new medications that coincided with his visual symptoms, these medications were investigated and will be discussed further.

His medical history included hypertension, hyperlipidemia, and a recent urinary tract infection. His current medication regimen included: alfuzosin HCL 10 mg for benign prostatic hyperplasia, finasteride 5 mg for benign prostatic hyperplasia, docusate sodium 50 mg/sennosides 8.6 mg for constipation, hydrochlorothiazide 25 mg for hypertension, venlafaxine HCL 50 mg for anxiety, zolpidem tartrate 5 mg for insomnia, and potassium phosphate 155 mg/sodium biphosphate 852 mg/sodium phosphate 130 mg, vitamin D3 1000 units, vitamin B12 1000 mg, and calcium 200 mg supplements. He had no known allergies to medications.

The patient's Snellen visual acuities measured 20/30+ in the right eye and 20/20- in the left eye at his eye examination 1 month prior. The 20/30+ acuity in the right eye was stable and attributed to a mild cataract. At the patient's full exam 8 months prior, his macular OCT scan showed normal foveal contour in both eyes. At presentation, his best corrected visual acuities were reduced to 20/50 in the right eye and 20/50- in the left eye. Refractive error was stable at +0.25-1.75 x 080 right eye and -0.50-1.50 x 105 left eye. Pupils were equal, round, and reactive to light without an afferent pupillary defect. Biomicroscopy of the anterior segment was unremarkable and intraocular pressures were 17 mm Hg in both eyes. A dilated eye exam revealed mild nuclear and cortical cataracts in both eyes. Cup-to-disc ratios of the optic nerve were 0.45 in the right eye and 0.2 in the left eye. Examination of the maculae showed patchy epiretinal membranes in both eyes with a faint 1/8 DD red foveal spot in the right eye (Fig 1). Vessels were of normal course and caliber in both eyes. The peripheral retinae were flat and intact.



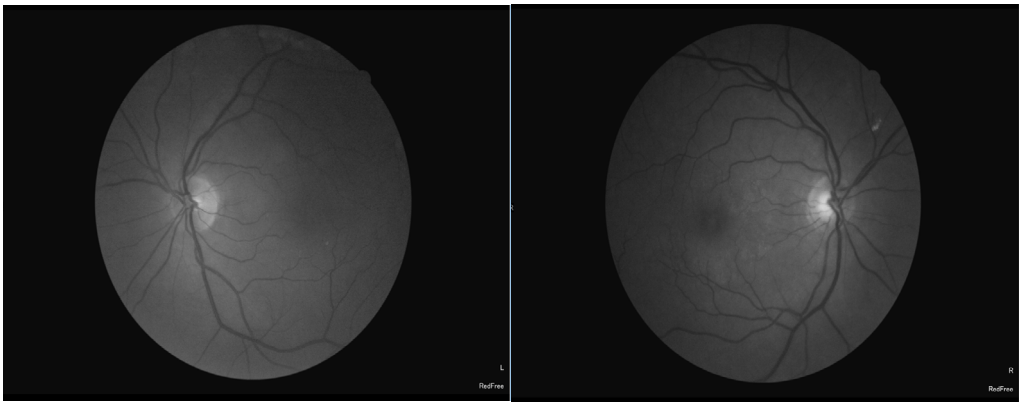


Figure 1: Color and red free fundus photographs of the right eye and left eye at the time of the small macular hole diagnosis, exhibiting mild epiretinal membrane in each eye and a subtle red foveal spot in right eye.

Spectral domain imaging of the maculae was obtained using the Zeiss Cirrus HD 5000 OCT to help reveal the cause of the reduced vision. Imaging showed vitreomacular traction and macular hole formation, with minimum hole widths measuring 107 microns for the right eye and 190 microns for the left eye. Based on IVTS staging, the patient was diagnosed with vitreomacular traction and secondary small full-thickness macular holes in each eye (Fig 2).

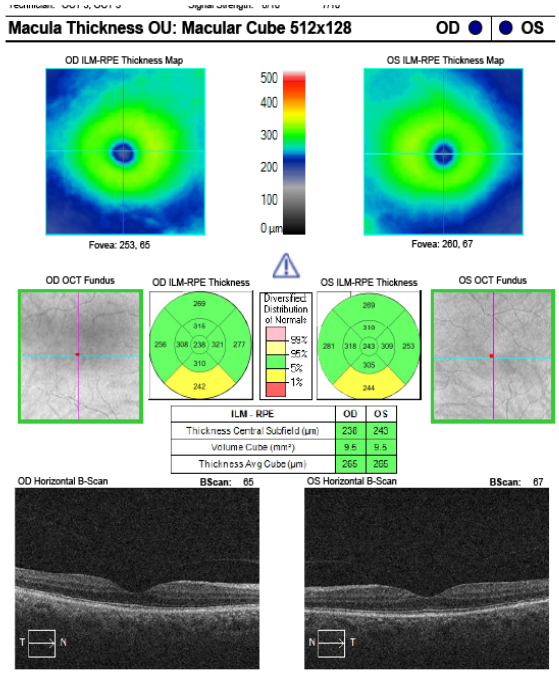


Figure 2: OCT macular cube scan at visit 8 months prior showing a normal foveal contour of each eye.

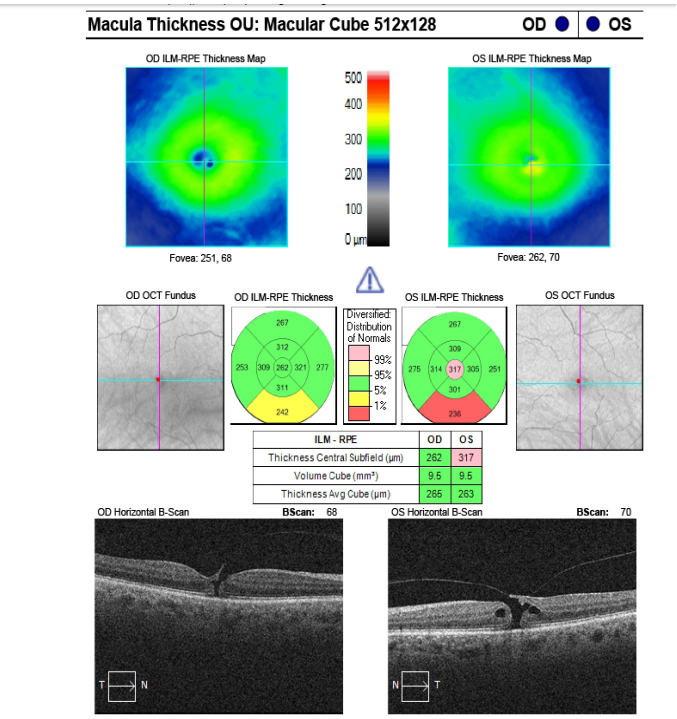


Figure 3: OCT macular cube scan of each eye at initial presentation showing vitreomacular traction with small full-thickness macular holes in the left eye more than right.

The patient was educated that he no longer met the state of Ohio nighttime driving standards of 20/40 vision or better in at least one eye. The patient agreed to the restriction of daytime only driving. An Amsler grid was dispensed for daily use and the patient was educated to call if sudden changes occurred while observing the grid. Given the concerning nature of bilateral macular holes which were affecting his quality of life, a referral was made to a retinal specialist for evaluation and management.

Due to the patient's chemotherapy schedule, the patient was seen by the retinal specialist 8 weeks after his initial optometry evaluation. His visual acuity was reduced to 20/100 right eye (pinhole 20/60) and 20/400 left eye (pinhole 20/200). The OCT HD 5-line raster scan showed resolution of vitreomacular traction, but progression to large full-thickness macular holes, left eye worse than right (Fig 4). A vitrectomy with epiretinal membrane peel and gas tamponade was recommended by the retinal specialist. Risks of vitrectomy, including cataract progression and residual distortion even after successful surgery were discussed. The patient was

agreeable to surgery. The surgical plan included a macular hole repair, starting with the right eye once he was given medical clearance by his oncologist.

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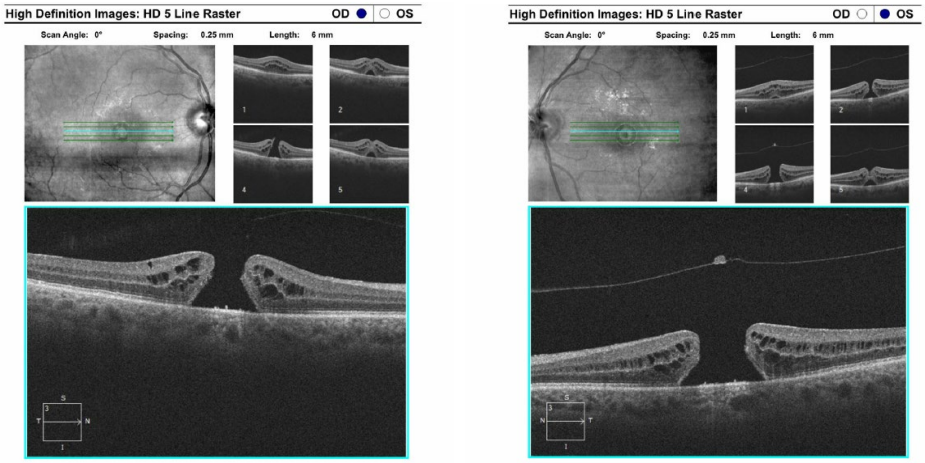

Figure 4: OCT HD 5 Line Raster of right eye and left eye at 8 weeks illustrating resolution of vitreomacular traction and progression to large full-thickness macular hole both eyes.

A shared clinical decision was made to postpone the retinal surgery until his chemotherapy was completed. The patient was seen for an office visit by the retinal specialist a few months later; acuities remained stable at 20/100 right eye and 20/400 left eye. The patient was now able to proceed with a vitrectomy the following week to repair the full-thickness macular holes, starting with the right eye.

The patient underwent a successful vitrectomy with an epiretinal membrane peel and gas tamponade of the right eye. He had good surgical results with a best-corrected visual acuity of the right eye measuring 20/40 at his 8 week post-operative visit. As shown in Figure 5, the OCT showed an anatomically closed macular hole.

The plan was to proceed with vitrectomy in the left eye during the next break in chemotherapy.

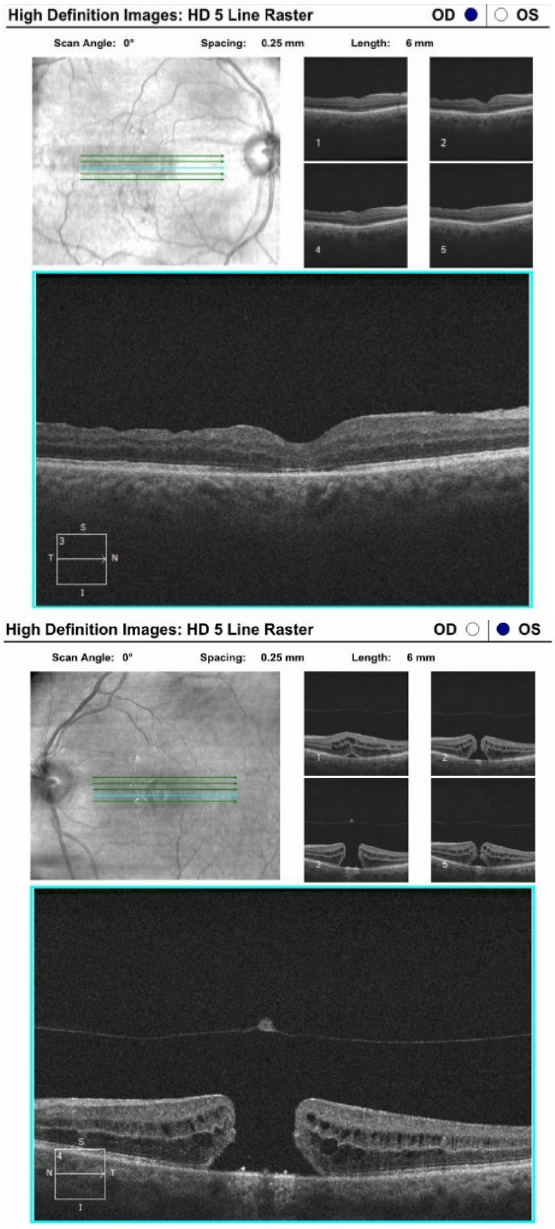

Figure 5: OCT HD 5 Line Raster right eye after vitrectomy with epiretinal membrane peel showing an anatomically closed macular hole, clear vitreous and residual retinal surface irregularity, in comparison to a large full-thickness macular hole left eye at 8 week follow up visit.

DISCUSSION

Our patient presented with the rare finding of new bilateral full-thickness macular holes while undergoing chemotherapy and radiation treatment for metastatic prostate cancer. The role of vitreomacular traction in the etiology of macular holes is widely known.[1] Risk factors of full-thickness macular holes include high myopia, trauma, ocular surgery, electric shock, and some systemic medications.[1,4] High myopia can lead to increased anteroposterior or tangential forces on the retinal surface. These tractional forces may predispose a patient to the formation of macular holes. Laser-assisted in situ keratomileusis (LASIK) surgery may induce postoperative changes in the vitreomacular interface due to the mechanical stretch of the vitreous produced by the suction ring.[4] This, combined with the shock waves generated by the excimer laser, may subsequently provoke macular hole formation.[4] It should be noted that many patients undergoing LASIK have an anatomic predisposition to macular holes given underlying high myopia.[4] There has also been evidence of bilateral macular holes after a patient was struck by lightning.[5]

Absent high myopia, LASIK, electrical shock, or recent trauma, it was necessary to investigate other causes, including medications and the patient's radiation history. Systemic medications, particularly those that may cause cystoid macular edema or increased vitreomacular traction, have been implicated in the formation of macular holes. Tamoxifen is a widely known chemotherapy agent linked to maculopathy. Tamoxifen is a selective estrogen receptor modular used for breast cancer treatment.[6] Eisner A et al proved that foveae of women using anastrozole (Arimidix®) appeared to be subjected to more tractional force than the foveae of women not using any hormonal medication.[7] Another treatment for breast cancer is docetaxel (Taxotere®) which has also been linked to maculopathy.[8] These chemotherapy agents are not used in the treatment of metastatic prostate cancer. A literature review did not yield any evidence of macular holes as known side effects of chemotherapy agents commonly used for males with metastatic prostate cancer nor any systemic medications prescribed for our patient.

Because of the dependence of most prostate cancers on testosterone, hormone therapy is used throughout various stages of prostate cancer. Our patient was prescribed the recommended dosage of enzalutamide, which is 160 mg/day.[9] Oral enzalutamide has been generally well tolerated in randomized controlled trials.[9] As seen in Table 2, enzalutamide has not been shown to have ocular side effects.[9] It is only recommended to use enzalutamide with caution in patients with a history of seizure, known cardiovascular risk factors and/or those who experience ischemic events.

Common adverse reactions (>10%):	Less common reactions (1% to <10%):	Rare reactions (less than 1%):
Asthenia/fatigue	Nonpathologic fractures	Seizure
Hot flush	Anxiety	Ischemic heart disease
Headache	Memory impairment	
Hypertension	Dry skin	
	Pruritus	
	Gynecomastia	

Table 2: Oral enzalutamide adverse reactions

Leuprolide acetate for injectable suspension (Eligard®) is used to treat the symptoms associated with advanced prostate cancer.[10] Leuprolide acetate is the first luteinizing hormone-releasing hormone agonist commercially available that extends treatment for 6 months.[11] It rapidly suppresses testosterone levels; after 1 month of treatment, 97% of patient had a testosterone level less than 50 ng/dl.[10] The mean time to testosterone suppression to 50ng/dl was 21.2 days.[10] A 12-month, multi-center clinical study was completed to investigate leuprolide acetate.[10] The most common adverse events include hot flashes, asthenia, and gynecomastia.[10] No ocular side effects were reported during this clinical study. [10]

To aid in analyzing the role of systemic medications on retinal findings, the Naranjo adverse drug reaction probability (ADR) scale was utilized.[11] To separate any interaction between enzalutamide and the Eligard® injection, both medications were scaled individually. Both medications received the same score and deemed as *possible* adverse drug reactions. For injectable medications like leuprolide acetate, the ADR scale may have some limitations. Unlike oral medications, an injected medication with a 6-month effect cannot be easily withdrawn. Thus, the scale should be cautiously interpreted for this case.

Radiation has been known to yield adverse ocular effects. Radiation retinopathy has been reported following local plaque radiation and external beam radiation for the treatment of ocular and periocular conditions such as choroidal melanoma, choroidal metastases from breast carcinoma, nasopharyngeal carcinoma, periorbital basal cell carcinoma, and intracranial lesions.[12] The manifestations of radiation retinopathy are frequently likened to the retinal vascular abnormalities of diabetic retinopathy such as microaneurysms, retinal hemorrhages, capillary non-perfusion, and infarcts of the nerve fiber layer.[12] Macular changes such as hard exudates, macular edema, and serous detachment have also been reported.[12] These macular changes, although less common, have the potential of leading to macular hole

formation. In our case, the patient's radiation treatments targeted the prostate and lower back, and therefore, less likely to have resulted in ocular complications.

Treatment of full-thickness macular holes begins with a referral to a retinal specialist. Superior surgical results are usually achieved in smaller lesions present for under 6 months; however, some substantial visual improvement has been seen in longstanding cases.[1] Referral is typically made within several weeks, sooner if quality of life is affected. The surgical treatment requires a vitrectomy combined with a peeling of the internal limiting membrane to relieve vitreomacular traction, and gas tamponade placement.[1] The need for extended face down positioning following the surgical repair has been questioned in recent years.[1] Our patient was referred for surgical treatment at his initial visit due to the impact the bilateral condition had on his activities of daily living. Given the patient's systemic health and potential effects of his chemotherapy treatment on his ocular health, surgical treatment was postponed until there was a break in chemotherapy treatment. After surgical treatment of the first eye, the large full-thickness macular hole was successfully closed. Vitrectomy with membrane peel and gas tamponade for the second eye was planned for the next break in his chemotherapy treatment.

CONCLUSION

Full-thickness macular holes can have a major impact on quality of life due to their rapid and significant impact on central vision. This is especially true on the rare occasion that they occur bilaterally. Most full-thickness holes occur unilaterally, secondary to vitreomacular traction, with occasional involvement of the fellow eye months to years later. The occurrence of simultaneous, bilateral full-thickness macular holes is rare, forcing the clinician to investigate other risk factors.

Our patient developed full-thickness macular holes while undergoing chemotherapy and radiation treatments for metastatic prostate cancer. However, lacking further scientific evidence, we cannot conclude that chemotherapy agents or radiation were directly related to the simultaneous development of bilateral full-thickness macular holes in our patient. As the prevalence of prostate cancer increases and these medications become more widely used, more adverse reactions may be seen in the future. The prescribing physician should consider reporting adverse reactions to the drug monitoring board in these cases. This case emphasizes the importance of a comprehensive health history, prompt diagnosis and communication between specialists. Fortunately, with timely referral and treatment, surgical repair can be quite impactful for these patients.

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