Primary Vaginal Lymphatic Malformation in A Child :Case Report and Literature Review

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Abstract

Here we reported the first Chinese case of primary vaginal and pelvic lymphatic malformations who was diagnosed during childhood.To date, 14 reports of the primary lymphatic malformations of perineum in children were reported worldwide, and only 3 patients had lesions involving the vagina characterized with chronic vaginal discharge or mucosal lesions

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest .

Keywords: primary lymphatic malformation$_1$, vaginal discharge$_2$, childhood$_3$, oral Sirolimus$_4$,sclerotherapy$_5$

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Statement on Consent for Publication

WH: data acquisition and drafting of the manuscript. WH and DY: diagnosis and treatment of the patient. WX: data acquisition. WL,LJ and WH: critical revision. All authors contributed to the article and approved the submitted version.

Statement on Ethical Approval and Informed Consent

The study involving human participants was reviewed and approved by Ethics Committee of Henan Children's Hospital.Written informed consent to participate in this study was provided by the participants' legal guardian.

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ABSTRACT

Here we reported the first Chinese case of primary vaginal and pelvic lymphatic malformations who was diagnosed during childhood.To date, 14 reports of the primary lymphatic malformations of perineum in children were reported worldwide, and only 3 patients had lesions involving the vagina characterized with chronic vaginal discharge or mucosal lesions in perineum,which was line with our report.This has great significance in clinical practice–for children with similar chief complaints and perineal physical examination findings, the diagnose of lymphatic malformation should be considered.For the very first time, we utilized sclerotherapy with Bleomycin combined with oral Sirolimus to control the progress of the disease in children.

INTRODUCTION

Lymphatic malformations (LMs) are the second most common type of vascular malformation(12%), following by venous malformations(70%)[1]. Primary vaginal lymphatic malformation is an extremely rare category of LMs. Due to atypical clinical manifestations and difficulties of differential diagnosis,vaginal lymphatic malformation could be easily misdiagnosed or neglected. Here,we reported the first Chinese case of primary vaginal and pelvic LMs who was diagnosed in childhood.The patient presented with chronic increased vaginal discharge as well as white granular projections in the hymen.There was a 4-year interval from the manifestation to the verified diagnosis.

Modern imaging technologies and refined interventional treatment strategies are now central parts in the multidisciplinary management of the LMs patients[2].In this case, for the very first time, we tried to utilize sclerotherapy with Bleomycin combined with oral Sirolimus to control the progress of microcystic vaginal lymphatic malformation in children.The results turned out to be desirable.

CASE DESCRIPTION

A 10-year-old Chinese girl with increased volume of vaginal discharge was hospitalized at the Department of pediatric gynecology in June 2020. By the time of hospitalization, the patient's medical history was 4 years. Initially, parents noticed the patient had vaginal secretions, like milky, thin discharge, odor,and the amount varies. Vaginal bleeding, pruritus, requent micturition, fever were not detected. With suspected vulvovaginitis, hygiene measures were suggested.Vaginal culture and testing for pathogen were administered with no positive findings.Then empiric antimicrobial treatment (oral amoxicillin) was given while symptoms were not relieved. Based on that, hysteroscopy was administered while no special findings was discovered.

Due to persistent discharge, the patient was referred to our department. At admission, vital signs as blood pressure, heart rate, respiration and pulse were within normal range.The patient's weight was 41 kg, height was 143.5cm.Physical examination showed breast development staging Tanner III and pubic hair staging Tanner I.No vulvar rashes, vulvar pigmented/nonpigmented lesions,masses,lichen sclerosis or labial adhesions were seen. Numerous white granular projections could be seen in the hymen,and milky, thin discharge in the vaginal opening(Figure 1A).During admission,vaginal secretions were about 150ml per day.No surgery/trauma history or estrogen exposure was reported by the patient.

Multiple diseases could lead to increased vaginal secretions in pubertal females.The most common were vulvovaginitis and vaginal foreign body.Furthermore,vaginal and vulvar tumors, vulvar skin conditions(eg,Hemangiomas,LMs),systematic illness(eg,Crohn disease),urinary tract abnormalities should be considered.

Based on that, further examinations were administered.Lab examinations showed that blood routine test, urine routine test, liver and kidney function, thyroid function were normal.Follicle stimulating hormone was 7.100 mIU/mL, and luteinizing hormone 5.980 mIU/mL, pituitary prolactin 35.870 ng/mL, estradiol 44.510 pg/mL, testosterone 0.150 ng/mL, progesterone 0.637 ng/mL.Tumor markers such as alpha fetoprotein, carcinoembryonic antigen and human chorionic gonadotropin were negative.Pelvic ultrasonography indicated that uterine and ovarian volumes increased to the thresholds for puberty.Hence, pelvic MRI were administered,which indicated vascular malformations,as multiple lamellar and corp-like abnormal signals can be seen around bilateral iliac vessels in the pelvic cavity, uterus, vagina and rectum, bilateral inguinal lymph nodes, and bilateral lateral iliac wings(Figure 2A).

With the consent of the guardian and the patient, "direct vaginal and pelvic lymphatic malformation angiography through lymph nodes and lesions guided by ultrasound and DSA " was performed under general anesthesia. A large amount of light yellow clear liquid was extracted.Then puncturing through the swollen lymph nodes in the groin and the hyperplasia mucous membrane inside the vaginal opening, and injecting contrast agent with high-tension injection.Pelvic and vaginal lesions were completely revealed in an hour–microcystic lymphatic malformation with partial abnormal lymphatic dilatation was confirmed,which was consistent with preoperative MRI outcomes.Until then, primary vaginal and pelvic LMs was clinically confirmed.

Sclerotherapy with Bleomycin was given during the operation.The vaginal discharge was about 1ml 24 hours after the operation, and was disappeared 3 days after.Sirolimus (1mg qd) was administered orally one week after surgery to prevent the recurrence of some microcystic lesios, which might not be achieved by sclerotherapy. In 1 month follow-up,the granular protrusions in hymen disappeared, as well as the vaginal discharge.In 8 month follow-up,no vaginal discharge was observed,while sporadic granular projections could be seen in the hymen(Figure 1B). Pelvic MRI was performed again which showed lesions were reduced than before, and no vaginal involvement was observed(Figure 2B). Sclerotherapy with Bleomycin was recommended, but was refused by the parents,so we adjusted the the oral dose of Sirolimus to 1mg bid. In 14 month follow-up, there was no recurrence of clinical symptoms, and pelvic MRI display was stable(Figure 2C).

Discussion

LMs can occur at any age, 65% are seen at birth, and 80% by 1 year[3] .LMs are rarely located in the female genital tract.To the best of our knowledge, there are only 14 reports of the primary lymphatic malformations related to perineum worldwide in children[4-17] (Table 1). Of these, most lesions involve the labia, only 3 patients had lesions involving the vagina[10,12,15]. A case of a 28-year-old female was reported being diagnosed as chylocolporrhea associated with primary lymphangiectasia, who presented with increased vaginal discharge since puberty[10].Another case was a Chinese female who presented with increased vaginal discharges since 3 years old with mucosal lesions in perineum, while the diagnose of was not made until 21 years old[15].Recently, Tang et al. described a 12-year-old girl with intermittent vaginal discharge for 10 years,while the main symptoms related to gastrointestinal tract due to intestinal lymphangiectasia with protein-losing enteropathy, and finally diagnosed as generalized lymphatic anomaly[12].Here,we reported the first Chinese case of primary vaginal and pelvic LMs who was diagnosed in childhood.

In this article,the patient was characterized as increased vaginal discharge and a large amount of white granular protrusions in the hymen.According to literature review and clinical findings of this case, almost all patients of primary vaginal LMs had chronic increased vaginal discharge or combined mucosal lesions in perineum[10,12,15].This has great significance in clinical practice–for children with similar chief complaints

and perineal physical examination findings, the diagnose of LMs should be considered.

The non-specific clinical picture, combined with the difficulties of diagnosis verification, lead to a long diagnostic period ranging from 2 to 40 years based on the literature review.Only 7 cases were reported with clinical symptoms presenting before the age of 10[6,8,9,12,14-16].In our case, there was a 4-year interval from the manifestation to the hospitalization in a specialized department where the diagnosis was verified.

As for diagnosis, most were made by pathology without MRI or CT examination in the earlier reported cases[4-9,13,16].With the progress of imaging technology, MRI was performed in most cases reported recently,which showed that lesions involved pelvic cavity, retroperitoneum, groin, spinal muscle, buttocks, uterus, rectovaginal septum, vaginal wall,beside the superficial part of the perineum[10,12,15].Therefore, it is speculated that the previously reported cases whose manifestations limited to the labia, may had the probability of missed diagnosis.According to recommendations from the International Society for the Study of Vascular Anomalies in 2015,ultrasound and MRI are the first-line imaging techniques for identifying, characterizing, and evaluating the anatomic extent of vascular malformations[18].In our case,MRI provided direct evidence to support the diagnosis of LMs.

Due to the development of technology and the new sclerosing agents, sclerotherapy has become the mainstream treatment of macrocystic and mixed LMs[2].However,as to microcystic type,the effect of sclerotherapy was not desirable[19].Recent progress in germline and somatic mutations that leading to activate known intracellular signaling pathways in LMs has advanced pharmacological interventions for the disease. mTOR Inhibitor Rapamycin (Sirolimus) could reduce the proliferation,as well as regulate the proliferation, migration and adhesion of lymphatic endothelial cells, so was tried to treat LMs[20].Several literatures reported its effectiveness in the treatment of complex vascular malformations, especially in diffuse microcystic LMs [21,22].The efficacy and safety of topical Sirolimus in the treatment of superficial vascular malformations in children has also been reported[23].

According to existing publications, surgical resection was usually utilized in early reported cases[18,7,8]. Laser therapy was used in 1 case[8].Follow-up time for the cases was usually very short or no follow-up was mentioned.In our case,to achieve maximum control of the lesion and to prevent recurrence, we decided to utilize sclerotherapy combing with oral Sirolimus.The clinical symptoms were well controlled after 14 months of follow-up.Pelvic MRI also indicated a reduction in lesions.This is the first case of primary vaginal and pelvic LMs treated with Bleomycin sclerotherapy combing with oral Sirolimus in children. The short-term effect is desirable without obvious adverse reactions.The proper dose of Sirolimus was very important to the disease control. Further studies with large sample size, multi-center, and long-term clinical follow-up were required to explore optimal treatment options.

FIGURE 1— (A) Numerous white granular projections in the hymen at admission. (B)Sporadic granular projections in the hymen in 8 month-follow up after treatment.

FIGURE2— MRI Manifestations of the patient. (A)At admission: Multiple lamellar and corp-like abnormal signals around bilateral iliac vessels in the pelvic cavity, uterus, vagina and rectum, bilateral inguinal lymph nodes, and bilateral lateral iliac wings. (B)8 month follow-up after treatment: lesions were reduced than before, and no vaginal involvement was observed.(C)14 month follow-up after treatment:MRI manifestation was stable.

TABLE 1— Reported cases of primary lymphatic malformations of perineum worldwide onset during childhood.

Case NO.	Age of onset(year)	Age of diagnosis (year)	Basis of diagnosis	Lesion site	Intervention	Prognosis	Reference
1	-	17	Pathology	Labium majus	Surgical	-	S C Gupta(4)

2	Puberty	17	Pathology	Labium majus	Surgical	-	Rashmi Bagga(5)
3	3	3	Pathology	Labium minus	-	-	Kamal Aggarwal(6)
4	13	15	Pathology	Labium minus	Surgical	No recurrence in 6 month follow-up	Takashi Watanabe(7)
5	7	16	Pathology	Labium majus	Laser	No recurrence in 2 years follow-up	Ryosuke Sasaki(8)
6	10	20	Pathology	Labium majus	-	-	Virendra N(9)
7	Puberty	28	MRI	Inguines, uterus, vagina	Low-fat diet	-	Mariam S(10)
8	13	13	-	vulva	Observation	-	Anastasia V(11)
9	2	12	MRI	Retroperitoneum,spinalmus-cle,rectovaginal septum, vagina	parenteral nutrition	-	Tang G(12)
10	14	15	Pathology	Labium majus	-	-	Oceane D(13)
11	10	50	Tc99m、CT	Perineum	Observation	-	Balasubramani P(14)
12	3	21	X-ray、Pathology	Pelvic cavity, vulva, groin	-	-	Li Xiaojie(15)
13	5	10	Pathology	Labium majus	Observation	-	Yu Nan(16)
14	15	17	Pathology	Labium minus	Surgical	No recurrence in 6 month follow-up	Yin Dong(17)
15	6	10	MRI	Vagina, around bilateral iliac vessels, inguinal region, uterus, and around rectum	Sclerotherapy +oral Sirolimus	No recurrence in 14 month follow-up	This case

"-" indicates "not mentioned".

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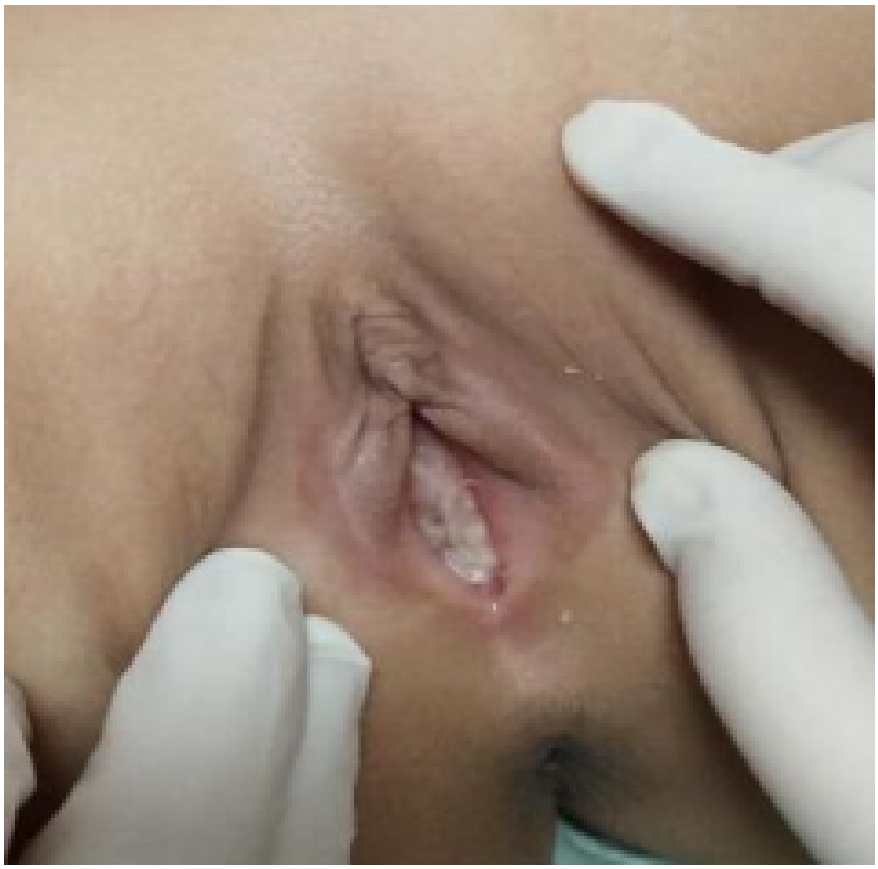

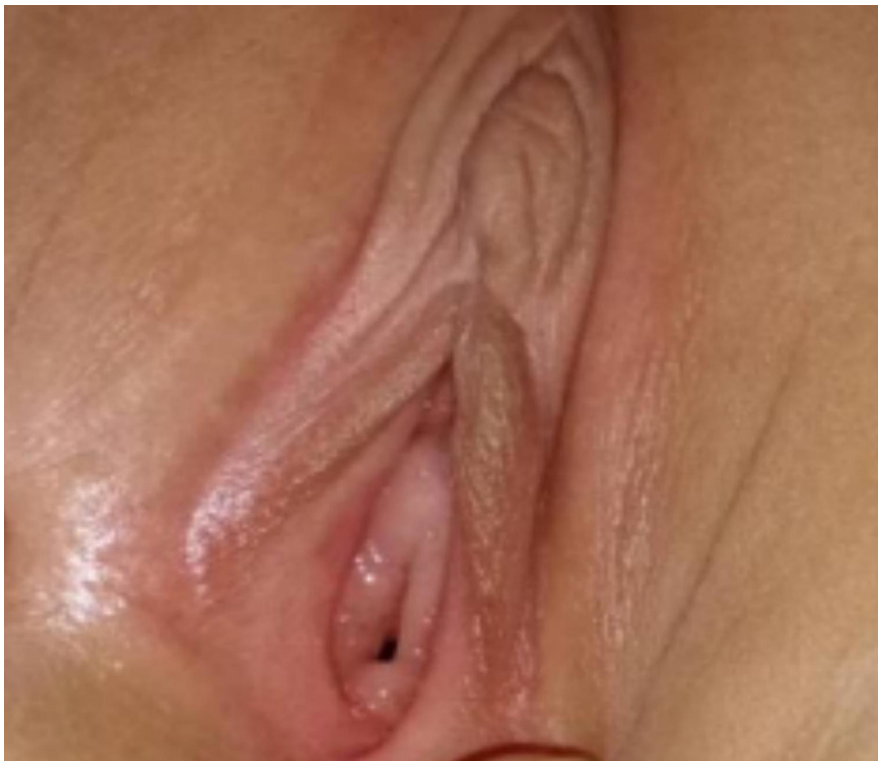

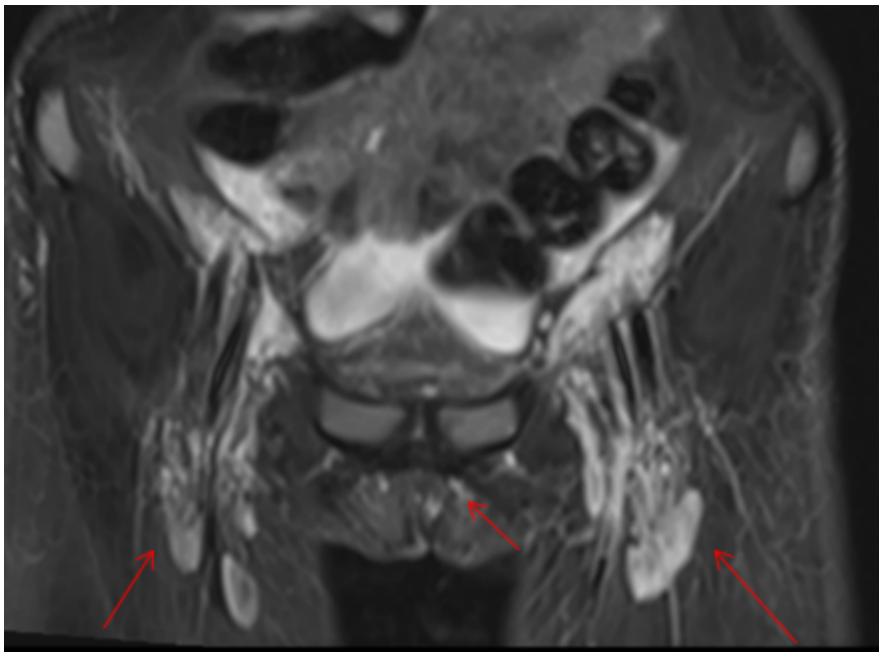

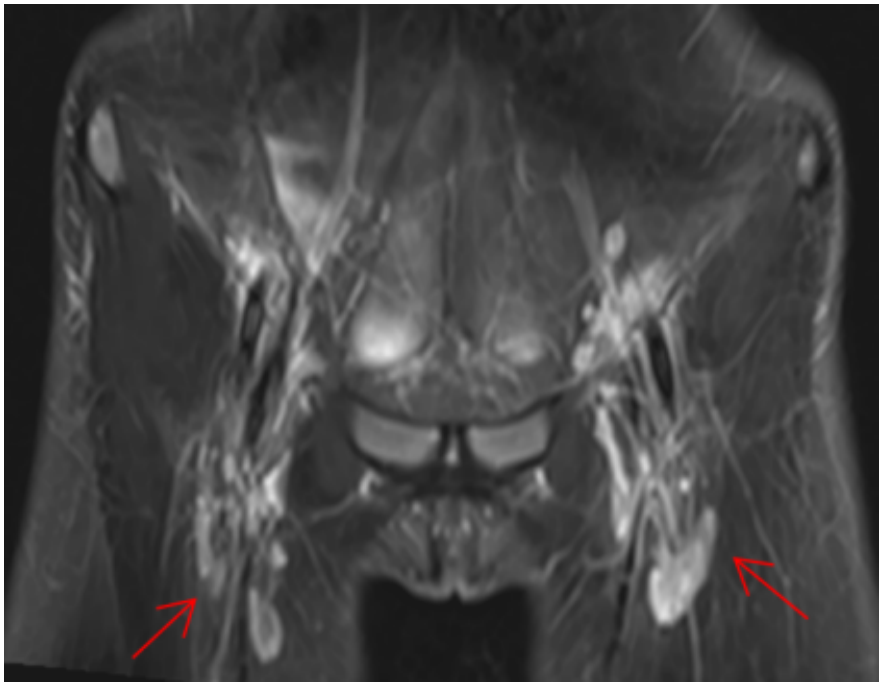

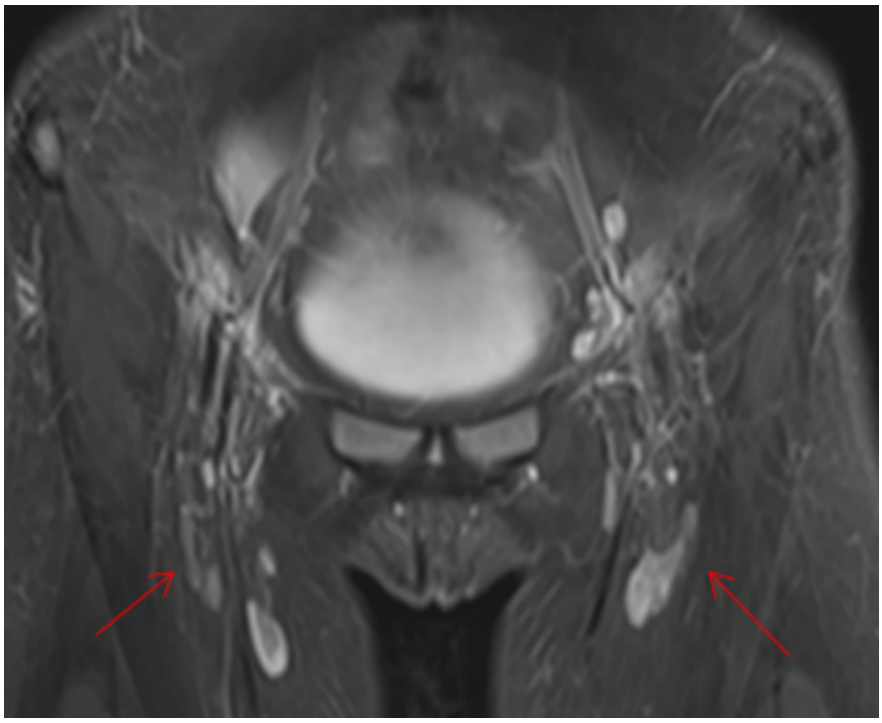

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