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ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Dr. Mukul Vij is Senior Consultant Pathologist and Lab Director at Dr Rela Institute and Medical Center in Chennai, India (since 2018). Having received his MBBS degree from King George Medical College in 2004, Dr. Vij undertook postgraduate training at Sanjay Gandhi Postgraduate Institute of Medical Sciences, receiving his Master's degree in Pathology in 2008 and his PDCC certificate in Renal Pathology in 2009. After 2 years as senior resident, he became Assistant Professor in the Department of Pathology at Christian Medical College, Vellore (2011), moving on to Global Health City as Consultant Pathologist and then Head of the Pathology Department (2013). (L-Editor: Filipodia)

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Inflammatory myofibroblastic tumor successfully treated with metformin: A case report and review of literature

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Abstract

BACKGROUND

Inflammatory myofibroblastic tumor (IMT) is a distinct tumor with a low incidence rate, which can be diagnosed at any age with a predilection for children and adolescents. Although IMT is visible in any tissues and organs, it is more commonly found in the lungs. The clinical and radiological manifestations of IMT lack specificity, hence resulting in frequent misdiagnosis. Surgical resection is currently the main therapeutic approach for IMT. Only scarce cases of IMT treated with metformin have been reported. Here we report the case of an IMT patient with partial penile resection treated with metformin.

CASE SUMMARY

A 1-year-old boy was born with a shorter penis, and his foreskin could not be completely turned over. When he was 6 month old, a well-circumscribed mass on the glans was found, while it did not attract the attention of his parents. The mass gradually increased in size over time before he was admitted to the hospital, where physical examination was performed. It was revealed that the glans hidden behind the foreskin had a mass with a diameter of about 4 cm surrounding the penis. The mass appeared to be hard with a smooth surface and poor mobility. The two testicles examined at the bottom of the scrotum were revealed to have a normal size. Magnetic resonance imaging showed a tumor with rich blood supply encircling the cavernosum with a size of 3.5 cm × 2.1 cm × 2.0 cm. A thick urinary line was found without urine dripping, urgency, and urodynia. Surgical treatment was performed. During the operation, it was observed that the mass had surrounded and invaded the cavernosum without obvious boundaries, and that the tumor occupied about one-half of the penis cross-section as well as infiltrated more than one-half of the glans. In addition, the tumor had caused urethral invasion and anterior urethrostenosis. With the intention of keeping the glans and cavernosum, the tumor at the anterior urethra was partially removed, leaving

conflict of interest to report.

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about 30% of the tumor mass. Pathology analysis demonstrated that the tumor was rich in spindle cells with infiltration of inflammatory cells. Immunohistochemistry analysis indicated that the cells were positive for CD4, CD99, Ki67, BCL2, and CD68, and negative for ALK, MyoG, S100, SOX10, PR, and EMA. Hence, the tumor was diagnosed as IMT. Metformin was prescribed for the patient after the operation, following which an oral dose of 7 mg/kg was given three times a day after meals. Three months later, it was observed that the remaining tumor had completely disappeared and that the urination process from the urethra opening had resumed normal. In addition, there were no side effects observed. There was also no tumor recurrence. The growth and development of the boy were unaffected as a result of the treatment.

CONCLUSION

The tumor was observed to have completely disappeared after treatment with metformin. Our finding is of great significance to facilitate future clinical treatment with IMT.

Key Words: Inflammatory myofibroblastic tumor; Metformin; Therapeutic; Case report; Adenosine phosphate protein kinase; mTOR

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Core Tip: Inflammatory myofibroblastic tumor (IMT) is a rare tumor in children, with surgical resection being the main treatment approach. We report a case of penile IMT with complete surgical resection. The residual lesions were found to have completely disappeared after treatment with metformin, a traditional drug.

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INTRODUCTION

Inflammatory myofibroblastic tumor (IMT) is a mesenchymal neoplasm of intermediate biological potential^[1]. Clinically, IMT occurs at any age and can affect any site of the body, although it is most commonly found in the lungs^[2,3]. IMT at early stages exhibits no obvious clinical symptoms. The pathogenesis of IMT is insidious and the etiology remains ambiguous^[4]. Currently, surgical resection is the first-line therapeutic approach, unless otherwise prohibited by the site of IMT being at a dedicative anatomic location, or by the occurrence of multiple lesions or complications^[5]. There have been studies reporting on cases that were prescribed corticosteroids for IMT^[6,7]. Here we report a case of penile IMT with incomplete resection treated with metformin. Surprisingly, the tumor was observed to have completely disappeared after metformin was administered for about 3 mo. Our finding may provide an alternative treatment approach for IMT.

CASE PRESENTATION

Chief complaints

A 1-year-old boy was born with a shorter penis, and his foreskin could not be completely turned over.

History of present illness

A round hard mass on the glans was found when he was 6 mo old, with a clear boundary and smooth surface. The mass gradually increased in size over time.

History of past illness

The patient had a free previous medical history.

Personal and family history

The patient and his family had a free previous medical history.

Physical examination

The glans hidden behind the foreskin had a mass with a diameter of about 4 cm surrounding the penis. The mass appeared to be hard with a smooth surface and poor mobility. The two testicles were revealed to have a normal size. A thick urinary line was found without urine dripping, urgency, and urodynia.

Laboratory examinations

There were no significant abnormalities in blood analysis.

Imaging examinations

Magnetic resonance imaging showed a tumor with rich blood supply encircling the cavernosum with a size of 3.5 cm × 2.1 cm × 2.0 cm (Figure 1).

MULTIDISCIPLINARY EXPERT CONSULTATION

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The patient should undergo surgical treatment and obtain histopathological results to confirm the diagnosis.

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The tumor should be removed as completely as possible to confirm the diagnosis. The patient could undergo chemotherapy when it is necessary.

Li YH, PhD, Professor, Department of Radiology, Xinhua Hospital, Shanghai Jiaotong University, School of Medicine

It is considered to be a fibroma based on the magnetic resonance image, but it still requires further pathological confirmation.

FINAL DIAGNOSIS

Surgical treatment was performed. After operation, pathology analysis demonstrated that the tumor was rich in spindle cells with infiltration of inflammatory cells (Figure 2). Immunohistochemistry analysis indicated that the cells were positive for CD4, CD99, Ki67, BCL2, and CD68, and negative for ALK, MyoG, S100, SOX10, PR, and EMA. Hence, the tumor was diagnosed as IMT.

TREATMENT

According to the past clinical experience, metformin (Sino-American Shanghai Squibb Pharmaceuticals Ltd., 0.5 g/tablet) was prescribed for the patient after the operation, following which an oral dose of 7 mg/kg was given three times a day after meals.

OUTCOME AND FOLLOW-UP

Three months later, it was observed that the remaining tumor had completely disappeared and that the urination process from the urethra opening had resumed normal (Figure 3). In addition, there were no side effects observed. There was also no tumor recurrence. The growth and development of the boy were unaffected as a result

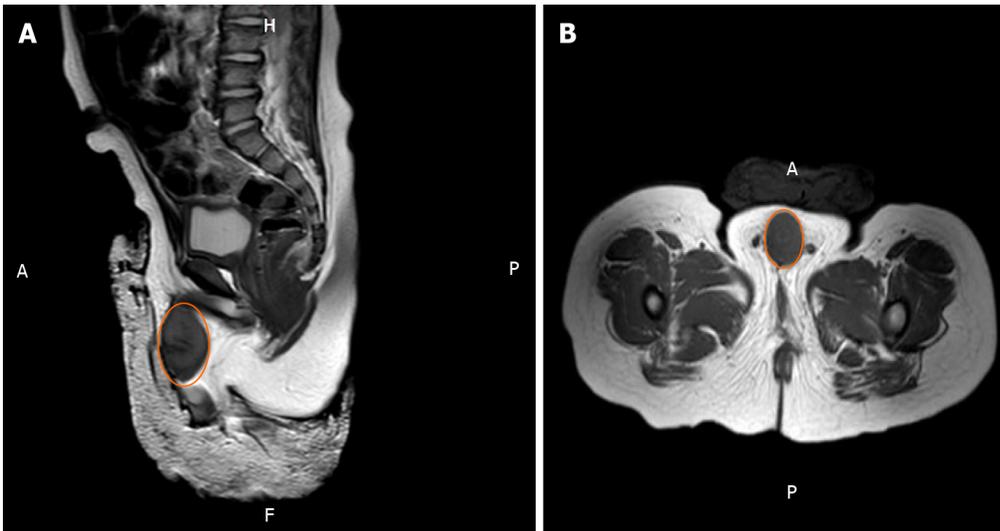


Figure 1 Magnetic resonance images of a tumor with rich blood supply encircling the cavernosum with a size of 3.5 cm × 2.1 cm × 2.0 cm. A: Coronal image; B Axial image.

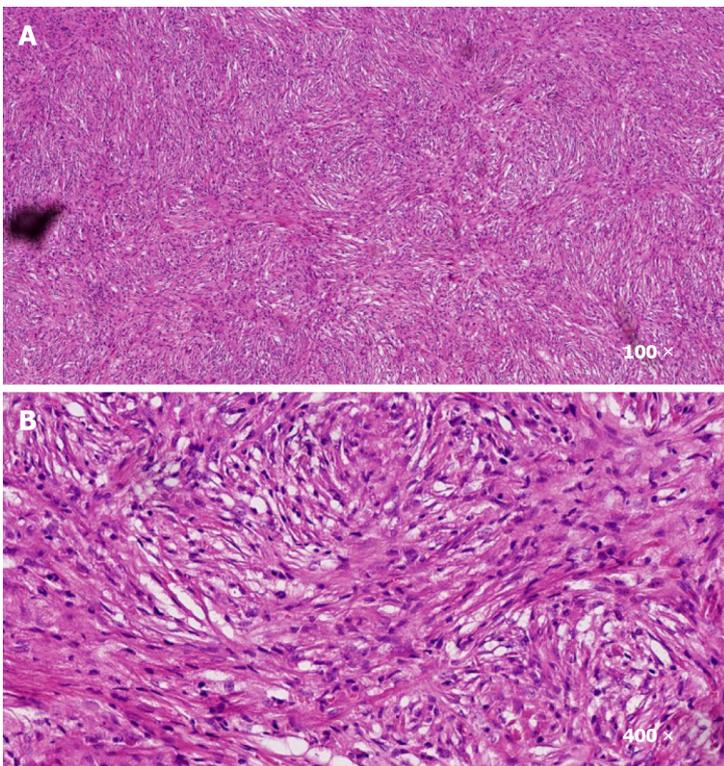


Figure 2 The tumor tissues at (A) 100 × magnification and (B) 400 × magnification stained with hematoxylin-eosin were rich in spindle cells with infiltration of inflammatory cells.

of the treatment.

DISCUSSION

IMT is a rare tumor commonly found in children and adolescents^[1,8]. Tissues of IMT comprise inflammatory cells and mesenchymal spindle cells^[9]. To date, the etiology of IMT is unknown, but it may be due to operation, trauma, radiotherapy, infection, the use of steroid hormone, and autoimmune reaction. Whilst about 50% of IMT patients have genetic translocation and rearrangement of the *ALK* (anaplastic lymphoma

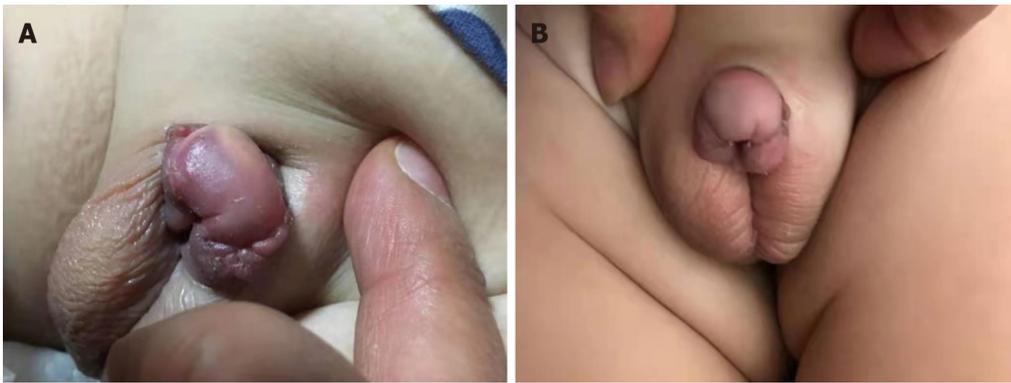


Figure 3 The tumor disappeared completely and the penis returned to normal (A and B).

kinase) gene on 2p23 that lead to the structural activation of tyrosine kinase and overexpression of ALK protein; the rest of IMT patients lack ALK expression^[10]. Although IMT can be found at any anatomical locations, it is commonly diagnosed in the lungs, abdomen, and pelvis. However, IMT is rarely found in the urogenital system. IMT usually presents an intermediate clinical behavior with the potential of recurrence. The rates of recurrence inside or outside of the lungs have been reported to be 2% and 25%, respectively, while the incidence of distant metastasis has been reported to be less than 5%^[11]. The radiological features of IMT vary, such as infiltration of inflammatory cells, interstitial fibrosis, and tumor distribution. Histopathological observation has indicated fibrous tissue hyperplasia, fibrous interstitial hyperplasia, and chronic infiltration of inflammatory cells, such as lymphocytes, plasma cells, and eosinophils. Immunohistochemistry analysis has demonstrated that IMT is positive for CD20, CD79a, CD3, CD45RO, SMA, vimentin, CD68, and Action (+), but negative for CD34, CK, and CD35. Although local surgical resection of IMT is recommended, preoperative or intraoperative biopsy is essential for clarifying the catalog of the tumor to avoid non-essential organ resection. It has been previously reported that IMT can be successfully treated using anti-inflammatory medications and glucocorticoids.

Several preclinical, epidemiological, and clinical studies have demonstrated that metformin, a first-line antidiabetic drug, can reduce the overall risk and mortality of neoplasms^[12-23]. Metformin is capable of inhibiting protein and lipid synthesis of tumor cells *via* the activation of adenosine phosphate protein kinase (AMPK) activity, which in turn downregulates the mechanical target of rapamycin complex 1 (mTORC1) signaling pathway, thereby limiting tumor growth and proliferation^[24]. Metformin can also suppress the oxidative phosphorylation of mitochondria, resulting in the decrease of ATP level, thus inducing the energy stress of tumor cells and making them vulnerable to energy crisis and cell death in the presence of some mutations^[25]. In addition, metformin can also inhibit tumor growth through the downregulation of insulin/IGF-1 levels, and the regulation of cell cycle and immune response. Nevertheless, the mechanism of metformin in the inhibition of IMT is ambiguous. To date, the main molecular targets of metformin are complex I of the mitochondrial electron transport chain, AMPK, and mTORC1. As a member of the conserved serine/threonine protein kinase from the phosphatidylinositol 3 kinase (PI3K) family, mTOR is the target of rapamycin. Regulated by nutrients and growth factors, mTORC1 is the main regulator of cell growth and metabolism *via* the phosphorylation of target cells. Due to the impacts on downstream oncogenesis, the activity of mTORC1 has been observed to be increased in several tumors^[26,27]. Wang *et al*^[28] have indicated that metformin can inhibit the activity of mTORC1 through a number of pathways in the suppression of tumor growth. On one hand, mitochondrial electron chain transport (ECT) produces ATP, which then leads to the downregulation of AMPK. With metformin acting directly on ETC and inhibiting ETC activity to decrease ATP synthesis, the resulting higher ratio of AMP/ATP induces the activation and phosphorylation AMPK, thereby leading to the inhibition of mTORC1^[29,30]. On the other hand, metformin can also activate AMPK and inhibit mTORC1 through a mechanism that is independent of the ECT^[26]. In addition, the activation of AMPK may repress myofibroblast differentiation through TGF- β 1^[31]. The activation of AMPK promotes the inactivation/apoptosis of myofibroblasts, which can also be found in other cells, such as alveolar epithelial cells and immune cells. Particularly, the activation of AMPK may also mediate the promotion of decomposition or anti-fibrosis,

thus inhibiting the proliferation of IMT^[32]. IMT is an extremely rare disease, and the available therapies have been underdeveloped.

CONCLUSION

Based on this case report, metformin as an easily accessible drug has been found to have the potential to become an ancillary treatment for IMT. However, it is essential to conduct randomized controlled trials with larger sample sizes to confirm our conclusion.

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