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Case and Review

Sirolimus in the Management of Blue Rubber Bleb Nevus Syndrome: A Case Report and Review of the Literature

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Abstract
Blue rubber bleb nevus syndrome (BRBNS) is a rare multifocal venous malformation (VM) that may affect any tissue or organ but mainly affects the skin, subcutaneous tissue and gastrointestinal (GI) tract. Patients present with serious anemia, treated with lifelong iron supplements and frequent blood transfusion secondary to chronic GI bleeding. Variable therapeutic modalities were used in the management of BRBNS; sirolimus (SRL), a mammalian target of rapamycin (mTOR) inhibitor, is found to be a promising therapy for vascular anomalies.

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Introduction

Blue rubber bleb nevus syndrome (BRBNS) is a rare multifocal venous malformation (VM) that may affect any tissue or organ, but mainly affects the skin, subcutaneous tissue and gastrointestinal (GI) tract. BRBNS might present at birth (30%), infancy (9%) or early childhood (48%) [1–3]. The syndrome is sometimes called Bean syndrome, after William Bean, who in 1958 was the first to characterize the lesions as compressible blue or purple cutaneous lesions with a diameter of 1–2 cm^2 that are asymptomatic and rarely bleed spontaneously but bleed easily upon trauma [4, 5]. Patients with BRBNS can develop coagulopathy with low fibrinogen and high D-dimer. In addition, they present with serious anemia, which can be treated with lifelong iron supplements and frequent blood transfusions secondary to chronic GI bleeding [1–3]. Some reported cases of BRBNS showed an autosomal dominant pattern of inheritance [6, 7], but most cases are sporadic. Variable therapeutic modalities are used in the management of BRBNS, including antiangiogenic agents such as corticosteroids and interferon-alpha, octreotide, sclerotherapy and aggressive surgery [1, 2, 5, 8–11]. According to multiple case reports, sirolimus (SRL), a mammalian target of the rapamycin (mTOR) inhibitor [1], has been found to be a promising therapy for vascular anomalies. Herein, we report the first Middle Eastern case in the literature: a patient with BRBNS that was successfully treated with sirolimus after the failure of several modalities of management.

Case Presentation

Our patient is an 18-year-old female who visited King Faisal Specialist Hospital and Research Center in 2004, where she was diagnosed with BRBNS involving the gastrointestinal tract, brain and skin. Her condition has been managed for many years with multiple modalities, including medical as well as chemotherapy (cyclosporine and vincristine) and interventional radiology performed by pediatric hematology oncology and radiology teams. Unfortunately, these measures failed to control her disease. In addition, because of gastrointestinal (GI) bleeding, the patient developed chronic anemia and since that time has been transfusion dependent on an almost weekly basis with no improvement of her hemoglobin. She would always present with low readings of WBC (2.0–3.8 $\times 10^9$//L), RBC (1.1–2.1 $\times 10^{12}$/L), hemoglobin (31–55 g/L) and platelets (112–140 $\times 10^9$/L).

In 2012, the patient travelled abroad where she had multiple surgical procedures, including surgical resection, laser and sclerotherapy of GI lesions, that resulted in complete control of her disease with no requirement of blood transfusions since. Part of her preventive management plan was sirolimus 1 mg (0.7 mg/m^2/day) PO, which resulted in improvement of her lab readings: hemoglobin (115 g/L), RBC (4.87 $\times 10^{12}$/L), platelets (176 $\times 10^9$/L) and WBC (4.21 $\times 10^9$/L). Since 2012, until her presentation to the dermatology clinic in 2017, the patient has been on sirolimus 1 mg PO daily.

However, the patient started to develop new lesions over her back and feet beginning 1 year prior. Therefore, in May 2017, when she visited the dermatology clinic, we adjusted the dose of sirolimus to 2 mg (1.4 mg/m^2/day). In subsequent follow-up visits, the patient's condition was improving with maintained hemoglobin and no development of new active lesions, except for low WBC (3.16 $\times 10^9$/L). Enhanced and non-enhanced magnetic resonance imaging (MRI) of the patient's head and neck were done in October 2017 and found that there was a

4-cm decrease in the size of the lesion on her lower left neck in comparison to her last MRI done in 2010.

Discussion

BRBNS is a rare vascular anomaly syndrome characterized by multifocal lesions consisting of venous malformations, which appear prominently in the GI tract, skin and soft tissues [1, 2]. As the patient grows, the number and size of lesions tend to increase [12]. One of the persistent complications of BRBNS is iron deficiency anemias due to chronic bleeding from GI lesions, which patients commonly experience at an early age. Therefore, patients require lifelong iron replacement, and in severe cases, regular blood transfusions might be required because of chronic anemias. This was true in our case, in which the patient had very low hemoglobin (31–55 g/L) and was thus receiving PRBC on a weekly basis.

Octreotide has been used in BRBNS, resulting in an improvement of symptoms with a decrease in transfusions over 12 months of follow-up, but repeated video capsule endoscopy revealed one case with no changes in the number and size of lesions [13]. Antiangiogenic agents, such as steroids, interferon-alpha and propranolol, were used, but the lesions failed to reduce in size and number when steroids were used alone. Furthermore, when steroids and interferon-alpha were used together, the lesions regrew after treatment was discontinued [13–15]. No convincing evidence has been reported for long-lasting effects from any pharmacological treatment. Laser photocoagulation and endoscopic removal have been tried, but without lifelong success [16]. Surgical removal is another modality of bleeding management in BRBNS, but it has been discouraged because of its aggressiveness and the probability that the excised lesions would regrow [2].

Sirolimus is a mammalian target of the rapamycin (mTOR) inhibitor. mTOR is a protein complex that contributes to several cellular processes, such as cell growth, cell survival and angiogenesis. Additionally, it has potent antineoplastic and immunosuppressive properties [17]. With our patient, hemoglobin levels normalized after starting sirolimus, with no need for further blood transfusions. We observed no adverse effects, such as hyperlipidemia, mucositis, diarrhea, hepatic damage, azotemia, proteinuria, anemia, thrombocytopenia, and recurrent or severe systemic infection [18], except for neutropenia.

The first published case report of sirolimus in the treatment of BRBNS was in 2012; it demonstrated the efficacy of sirolimus at low doses to treat skin lesions and reduce GI bleeding after the failure of numerous management modalities [16]. In the past few years, multiple cases of BRBNS managed with sirolimus were reported to exhibit positive effects [1, 12, 16–19].

To our knowledge, our case represents the first case in the Middle East to show the efficacy of sirolimus in treating chronic iron deficiency anemia in BRBNS.

Conclusion

BRBNS is a rare multifocal VM that most commonly affects the skin, subcutaneous tissue and GI tract. Commonly used therapeutic modalities to treat BRBNS include corticosteroids, interferon-alpha, octreotide, sclerotherapy and aggressive surgery. However, these modalities often fail to produce long-lasting effects or are unfavorable due to their aggressive nature.

Herein, we conclude that sirolimus gives a promising response in treating BRBNS refractory to other treatment modalities and helps to avoid an aggressive surgical approach.

Statement of Ethics

A signed consent was provided by the patient to publish this case. The study protocol was approved by the institute's committee.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Bayan Musaed Alnooh (writing of the manuscript), Nada Ghazi Alqadri (writing of the manuscript), Muhtadi Alghubayn (writing and editing of the manuscript) Saad Alajlan (writing and editing of the manuscript).

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