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Case Report

Treatment of Refractory Polyarteritis Nodosa with Adalimumab

Hani Almoallim *ABIM, FRCPC (Internal Medicine & Rheumatology), DipMedEd (Dundee)*
Medicine Department, Umm Alqura University, Medical College, Saudi Arabi
Medicine Department, King Faisal Specialist Hospital, Jeddah, Saudi Arabia
hanialmoallim@hotmail.com
P.O.Box 1821, Jeddah 21441 Saudi Arabia
Tel: 00966-505-703935
Fax: 00966-26076080

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علاج مرض إلتهاب الشرايين العقدي المستعصي بالأداليموماب

هاني المعلم
أستاذ مساعد- قسم الطب الباطني- كلية الطب- جامعة أم القرى- مكة المكرمة
مستشفى الملك فيصل التخصصي ومركز الأبحاث- جدة –إستشاري الأمراض الباطنية والروماتيزم
الزمالة الكندية والأمريكية في الطب الباطني وفي طب الأمراض الروماتيزمية
hanialmoallim@hotmail.com
ص .ب 1821 جدة 21441

الملخص العربي

هناك العديد من التقارير الطبية المتزايدة عن نجاح إستخدام عقارات مضادات (ت ن ف- ألفا)وتحديدا مضادات أحاديِّ النسيلة كعقار الإنفليكسيماب في علاج حالات إلتهاب الشعيرات الدموية الدقيقة المستعصية. يصف هذا التقرير حالة شاب سعودي عمره 18 سنة فقد أنامله التي أصابتها الغر غرينا منذ 7 سنوات بسبب مرض إلتهاب الشرايين العقدي. إستجاب مرضه بداية لعلاج الستيرويد والسايكلوفوسفمايد، بعد ذلك تم وضعه على علاج الميثوتريكسات. ولقد كمن المرض لمدة 3 سنوات. حدثت انتكاسة بعد ذلك وعولجت بالميثايل بريدنيزولون العالي الجرعة الوريدية ومن ثم علاج الستيرويد الفموي وعلاج الميثوتريكسات، ثم تلا ذلك علاج الميكوفينولات. نتج ذلك عن استجابة غير كافية مع تعدد الانتكاسات المرضية. إن إستخدام عقار الأداليموماب بعد ذلك نتج عن إختفاء كلي لجميع العقد تحت الجلدية، بالإضافة إلى ذهاب الإسوداد الحاصل في أصابع القدمين مع عودة(معامل س النشط) إلى معدله الطبيعي.

ABSTRACT

There are an expanding number of reports on the successful use of anti-TNF-α agents, particularly monoclonal antibodies like infliximab in refractory primary systemic vasculitis. This report describes an 18-year-old Saudi boy who lost his gangrenous fingers 7 years ago from polyarteritis nodosa. His disease responded initially to steroid and cyclophosphamide then he was maintained on methotrexate. His disease was in remission for 3 years. His relapse was treated with methylprednisolone pulse therapy, prolonged use of oral steroid and methotrexate followed by mycophenolate mofetil. There was inadequate response with multiple flare up episodes. The use of adalimumab resulted in complete absence of all subcutaneous nodules, resolution of blackish discoloration of his toes and normalization of C-reactive protein value.

Key words: polyarteritis nodosa, refractory vasculitis, adalimumab, Anti-Tnf-alpha therapy

INTRODUCTION

In many of the vasculitides, disease relapse occurs frequently and patients continue to experience a high degree of morbidity and even mortality. Many therapeutic modalities have been described to treat refractory cases. There are an expanding number of reports on the successful use of anti-TNF-α agents, particularly monoclonal antibodies like infliximab (human chimeric anti-TNF-α monoclonal antibody) in refractory primary systemic vasculitis[1,2]. We report a case of refractory polyarteritis nodosa (PAN) in an 18-year-old Saudi boy that responded successfully to adalimumab.

CASE REPORT

An 18-year-old Saudi male patient presented to our hospital in November 2002 with blackish discoloration of fingertips for one-month duration. He also complained of migratory joint pains involving elbows and knees without joint swelling or redness. There was a high-grade fever, generalized myalgias, fatigability and poor appetite. He had no other symptoms and there was no hepatitis exposure. He had scattered subcutaneous nodules in several parts of his body. He was admitted for around a month where he was investigated thoroughly and received intravenous (IV) methylprednisolone (MP) pulse therapy in addition to IV cyclophosphamide. This had resulted in partial control of his pain, generalized fatigability and significant weight loss. During hospitalization, the livedo reticularis with the ischemic changes of his distal phalanges had progressed to gangrene formation and gradual self-amputation of all 10 fingers. The diagnosis of PAN was made based on clinical grounds and conventional angiogram conducted in November 2002. Angiogram demonstrated very poor flow into the radial and ulnar arteries bilaterally with almost no flow to the palm arteries. There was normal flow of cerebral and lower extremity arteries bilaterally. All serological tests for hepatitis and antineutrophil cytoplasm antibodies (ANCA) were negative. He was maintained on oral steroid and methotrexate (MTX) at 10 mg per week and responded well to treatment and remained asymptomatic. He stopped all

his treatment in August, 2005. In January 2008, he presented to our hospital with bilateral lower limb pain, swellings and redness with multiple subcutaneous nodules, erythema and livedo reticularis. There were ischemic changes over his toes. He was admitted to the hospital and received IV MP pulse therapy and maintained on 15mg MTX per week. His oral steroid dose was tapered over 3 months period. He did not observe total resolution of his symptoms but rather improvement of his pains with decrease in the size of the nodules. He presented again in May, 2008 with flare of his symptoms including profound pain and ischemic changes affecting his toes with blackish discoloration. C-reactive protein (CRP) was elevated at 77 mg/l. This was despite being on MTX 15 mg per week. He was admitted to the hospital and pulsed with IV MP again then was maintained on oral steroid and switched to mycophenolate mofetil (MMF). There was improvement initially especially following steroid pulse therapy. The dose of MMF dose was escalated rapidly to 2.5 grams per day. However, it was difficult to taper down his steroid dose due to incomplete resolution of his symptoms with episodes of flare up that necessitated delaying the tapering regimen. His CRP was always elevated above 68 mg/l despite being on variable doses of steroid and MMF. In June, 2009 anti-TNF-alpha therapy was considered during a regular clinic visit due to refractory symptoms of myalgias, subcutaneous nodules with lower limb erythema and livedo reticularis. His urinalysis and renal function were always normal and there were no respiratory or gastrointestinal symptoms. His PPD skin test was negative and chest x-ray was normal. Adalimumab 40 mg subcutaneously every two weeks was considered as a treatment modality for a refractory PAN. There was a minor response after two injections but all subcutaneous nodules disappeared completely after the fourth injection. The patient became asymptomatic, off steroid and CRP dropped for the first time to 3.57mg/l. His MMF was maintained at 2g/day. He remained asymptomatic with disappearance of flare up episodes that he used to complain of and normal CRP for 9 months after initiation of adalimumab.

DISCUSSION

Managing refractory systemic vasculitis is challenging. Infliximab (human chimeric anti-TNF-α monoclonal antibody) is reported in a recent case series to be efficacious in refractory primary systemic vasculitis[1] but none of the patients included in this report had PAN. There are few reports addressing the effective use of infliximab in PAN[3-5]. It is noted that the use of infliximab in PAN is usually indicated after evidence of relapse and poor response to several therapeutic trials. In one report, there was extensive gastrointestinal involvement with subcutaneous findings and protienurea. Several therapeutic trials including cyclophosphamide, methotrexate and IV immunoglobulins were used before considering infliximab[4]. In a retrospective case series of children aged 2.4-16 years with primary systemic vasculitis treated with biologic therapy, 11 out of 25 were diagnosed with PAN and had received other immunosuppressive therapies prior to biologic therapy[2]. There were 8 patients with PAN in this case series received infliximab and 3 received etanercept. Adalimumab was used in one patient with PAN after escaping initial efficacy from infliximab. Overall, there was a significant reduction in Birmingham Vasculitis Activity Score (BVAS) accompanied by significant reduction in median daily prednisolone

requirements. Adalimumab (a fully humanized IgG1 anti-TNF-α monoclonal antibody) was the agent used in this patient instead of infliximab. This was based on patient's social condition as he lives in a distant city and not willing to accept intravenous infusions.

ANCA-associated systemic vasculitis (AASV) has different disease pathology than polyarteritis nodosa. There is a lack of adjunctive efficacy of etanercept (a fusion protein of the p75 TNF-α receptor and IgG1) demonstrated in a clinical trial in adults with Wegener's granulomatosis (WG)[1]. Similar findings were reported recently with the addition of adalimumab to standard therapy of prednisolone and cyclophosphamide for the treatment of severe AASV[7]. However, there are reports on the successful use of adalimumab in various non-AASV disorders[8-11].

There is a growing interest in the use of MMF in ANCA-associated vasculitis. It can be used to induce remission especially in patients who cannot be treated with cyclophosphamide[12-14] or to maintain remission[15]. There is a very limited experience with MMF in PAN. In the case presented, there was no acceptable response when MMF was used in a dose of 2.5gm/day for almost 12 months. However, MMF was maintained in a dose of 2gm/day with the standard dose of adalimumab.

The diagnosis of PAN in the case presented here was based on clinical presentation that was highly suggestive of this type of medium-vessel vasculitis. At least 3 features of the American college of Rheumatology 1990 criteria for the classification of polyarteritis nodosa were met[16]. There was exclusive involvement of arteries based on angiogram findings with sparing of veins. There was no evidence of glomerulonephritis or pulmonary capillaritis and no associated autoantibodies like ANCA. In spite of the lack of histopathological findings in the case presented, most of the features presented otherwise meet the description of PAN provided by the Chapel Hill Consensus Conference that differentiates clearly between PAN and microscopic polyangiitis (MAP) [17].

TNF-targeted therapies are being used for a rapidly expanding number of rheumatic and autoimmune diseases. This resulted in a new spectrum of clinical adverse events one of them is the development of vasculitis. Leukocytoclastic vasculitis was the most frequent type in one report[18]. Systemic involvement has been reported as well[18-20].

We report a case of aggressive PAN that resulted in loss of all fingers. The patient used to have recurrent relapses in a form of painful subcutaneous nodules, myalgias, lower limb erythema with livedo reticularis and blackish discoloration of toes. There was no adequate response with the use of MTX and MMF in addition to prednisolone while treatment with adalimumab resulted in a successful response. The use of anti-TNF-α in PAN should be limited to refractory cases. Clinicians should be aware that vasculitis can be induced by anti-TNF-α agents. Further controlled studies are needed to address the role of anti-TNF-α agents in treatment of PAN.

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