Rituximab therapy for flare-up of rheumatoid arthritis after total knee replacement surgery

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Abstract

A variety of drug types are used alone or in combination to manage Rheumatoid Arthritis along with physiotherapy. We report herein the case of a 51 year old female patient with a history of Rheumatoid Arthritis whose disease remained active despite being on routinely used multiple disease modifying antirheumatic drugs. The patient underwent bilateral total knee arthroplasty with subtotal synovectomy due to the severe pain caused by her concomitant age related osteoarthritis which was only aggravated by her active rheumatoid arthritis disease. Three months following surgery, the patient's knee pain with typical rheumatoid flare and swelling reappeared for which a B cell monoclonal antibody, rituximab, was given. Her number of tender and swollen joints reduced to less than three and her C- reactive protein levels and erythrocyte sedimentation rate reduced significantly along with considerable improvement in her Global Assessment score. Her severity of pain also decreased to 3 from an initial score of 8 on the Visual Analog

Scale. Thus, Rituximab helped improve our patient's symptoms from recurrence of synovitis after total knee replacement.

Keywords: Total knee arthroplasty, Rheumatoid arthritis, Rituximab.

Introduction

Rheumatoid arthritis (RA) is a chronic, autoimmune disease mainly affecting joints but can have involvement of other organ systems. It results in the progressive destruction of the involved joint accompanied by distortion and failure of function. It has been known to affect approximately 0.5% to 1% of the adult population in the developing world.[1] In a recent study, in accordance with the criteria established by the American College of Rheumatology (ACR) in 1987, prevalence in Karachi was found to be 0.9 to 1.98 per thousand people.[2]

As per the ACR guidelines, the current therapies approved by Food and Drug Administration (FDA) for RA are a variety of drug types including non-steroidal anti-inflammatory drugs, glucocorticoids, disease modifying antirheumatic drugs, (DMARDS) such as methotrexate, hydroxychloroquine and sulfasalazine, immunosuppressive preparations, interleukin-1 blocker (anakinra), interleukin-6 blocker (tocilizumab) and biological agents such as anti-TNF agents (infliximab, certolizumab pegol, etanercept, adalimumab) and monoclonal antibodies against B cells (anti-CD 20 such as rituximab), used alone or in combination to conservatively manage RA along with physiotherapy. It has also been established that the use of uninterrupted physiotherapy combined with drug therapy to control RA in "postoperative" management of total joint arthroplasty has a more effective outcome in restoring the range of motion, diminishing joint swelling, alleviating symptoms and improving the overall prognosis.[3] Total Knee Arthroplasty (TKA) has a positive secondary systemic effect on disease activity in Rheumatoid Arthritis but it does not have a continuously encouraging outcome on the health-related quality of life.[4]

This case reported, is the first in South Asia, where rituximab has been used within three months following total knee arthroplasty (TKA) for active RA, with successful recovery of the patient without any complications of infections or septic arthritis.

Case:

A 51 years old female, known case of rheumatoid arthritis for the past 6 years, initially presented with pain in knees bilaterally which was reported to increase with movement and weight bearing. She later developed pain in small joints of hands and feet with bilateral joint swelling and morning stiffness in the involved joints lasting a few hours.

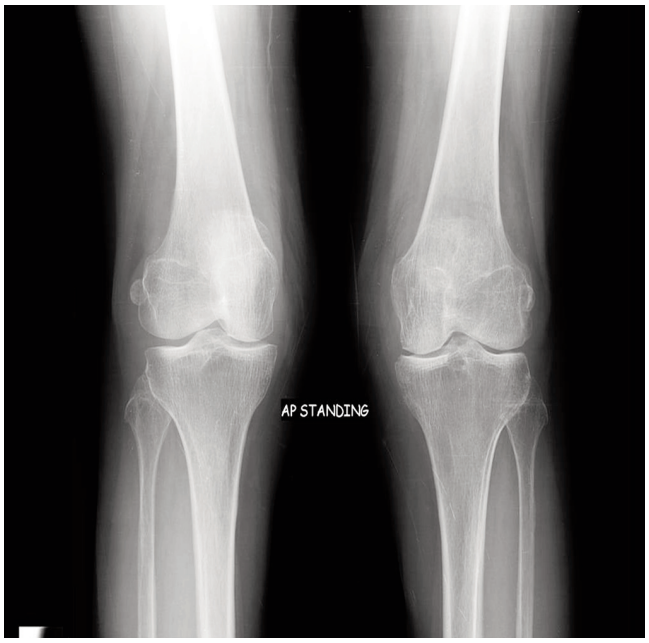

Figure: FINDINGS: Arthritic changes noted in both knee joints with osteophyte formation of both femur. Periarticular osteopenia noted. Symmetric joint space narrowing and sclerosis bilaterally.

The lab reports of the patient persistently showed raised C- reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR) levels were between 50-60mm/hr since the past three years. She had chronic anaemia and was found to be positive for rheumatoid factor and anti-cyclic citrullinated peptide antibodies (anti-CPP) with high titres.

General physical examination and systemic examination was normal. Examination of both hands showed metacarpophalangeal tenderness and that of both knees demonstrated tenderness and crepitus. Range of movement in the knees was decreased bilaterally. Radiographs of knee joints showed symmetrical joint space narrowing and periarticular osteopenia and sclerosis bilaterally (Figure).

The symptoms had been ongoing for the past 6 years for which she was given a trial of different anti rheumatic drugs such as DMARDS (methotrexate, sulfasalazine, leflunomide) and NSAIDs with intermittent steroids. The above medications did not put the patient in remission. Her knee pain aggravated because of concurrent osteoarthritis, limiting her daily activities.

It was then decided that the patient should undergo TKA for the relief of symptoms. Sections of synovium obtained in the course of her subtotal synovectomy during the TKA procedure from both the knee joints were sent for pathological review which showed multiple areas of benign fibromuscular and adipose tissue covered by inflamed

synovium composed predominantly of lymphocytes and admixture of granulation tissue reiterating an inflammatory pathology consistent with RA and also correlating with previous radiology reports.

Within three months following TKA, the patient's knee pain reappeared with the typical RA flare and swelling. Taking into consideration the patient's past history of unresponsiveness to the other therapies, rituximab was given. Prior to initiating rituximab therapy however, the patient was screened for hepatitis B and C, as well as for tuberculosis. Rituximab was given intravenously as two 1g infusions (with 100mg glucocorticoid intravenous premedication), separated by two weeks. After she received the first cycle of rituximab following TKA, a subsequent cycle with similar dosing was repeated in the next six months. In the following months, the number of tender and swollen joints in the patient reduced to less than three and her CRP and ESR reduced to 0.5 mg/dL and 18mm/hr respectively. There was also considerable improvement in her Global Assessment score. Her severity of pain also decreased to 3 from an initial score of 8 on the Visual Analog Scale. She recovered uneventfully and achieved remission with no evidence of infection and septic arthritis.

Discussion

Rheumatoid Arthritis is primarily a T cell mediated disease but B cells are also implicated in the pathogenesis. Anti-B cell therapy, such as rituximab, targets to remove B cell clones accountable for the assembly of pathogenic auto-antibodies. The objective is to induce persistent remission from transient B cell depletion, based on the proposition that auto-antibodies can produce tissue pathology as well as stimulate their own production through a vicious cycle.[5]

Reconstructive surgery should be considered, depending upon the joint, when medical therapy fails to control RA, the chief indication for surgery being severe joint pain either with movement or at rest. Total joint arthroplasty has significant success. The reported success rate for total knee arthroplasty is in excess of 85% at 10 years in patients with RA.[6] The aim of surgery in the treatment of RA is the relief of pain and the restitution of joint activity. When indicated, surgery is advised to be conducted in a timely manner because an extended delay can lead to permanent deformities, soft tissue contractures, or excessive muscle atrophy.[7]

There have been previous reports of using biological agents such as infliximab after TKA in not only attenuating the severity, signs and symptoms of active RA but in reducing the post operative complications in patients recovering from TKA.[8] Worldwide, more than 100,000 patients have received rituximab to date for RA.[9] However, we could not find any case report in our pubmed literature search where rituximab was used in patients following TKA.

Rituximab leads to rapid B cell depletion and is licensed and well established for patients with non Hodgkin lymphoma.[9] Rituximab has also been approved by the United States FDA and the European Medicines Agency in Europe for the treatment of patients with RA (with proven efficacy in RF positive patients) who have had inadequate response or were intolerant to available TNF inhibitors[9] It has been also advocated that infusing rituximab with intravenous glucocorticoids premedication will produce an early response (average 8 weeks as compared to 16 weeks[9] and reduce the frequency and intensity of first infusion-associated adverse events as addressed in the placebo-controlled DANCER trial.[10]

Hence, rituximab either used in combination with a glucocorticoid or used alone has established effectiveness in the treatment of aggressive RA and is also cost effective when compared with a TNF inhibitor.[9] Most common side effect of rituximab are fever, rigors, chills, numbness, muscle or back pain, headache, runny nose, weight gain, heartburn, fatigue, nausea and vomiting.[11] It should however be noted that rituximab is contraindicated in pregnancy and in patients with active infections and severe heart failure.[9]

Conclusion

Our patient is the first case reported in the available literature who received rituximab within the first three months after TKA to which she responded well. There were no signs of complications, most importantly infections, following this treatment. The use of rituximab in this patient expedited recovery from TKA by reducing disease inflammatory load and joint pain and also helped counteract the RA flare and swelling that the patient developed three months after her surgical procedure. Consequent to the treatment with rituximab, our patient was able to undergo intensive physiotherapy and hence recovered soon. Hence we can say with our experience with the aforementioned case that the use of biologic agent rituximab helped in easy recovery of RA after her TKA and the patient did not suffer from any feared complication of infections.

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