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Treatment of Pemphigus Vulgaris in a Patient with Avascular Necrosis using Cyclophosphamide

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Abstract

Pemphigus vulgaris is an autoimmune vesiculobullous disease of the skin and mucous membrane. Large dose of steroids and prolonged treatment is required to suppress and cure the disease. This leads to various side effects one of which is Avascular Necrosis (AVN). In dermatological practice AVN has been reported more commonly with steroid use for SLE and less commonly in Pemhigus. To decrease the exposure to corticosteroids use of steroid sparing drugs have gained importance. We present a case a 54 year old male having Pemphigus vulgaris with AVN of femoral head on right side secondary to high dose corticosteroids. Patient has been treated successfully with cyclophosphamide alone.

Keywords: *Pemphigus, AVN, Cyclophosphamide*

Introduction

Before the use of Dexamethasone Cyclophosphamide Pulse (DCP) treatment, corticosteroids alone were the mainstay of treatment. Avascular necrosis however still remains a crippling side effect of steroids which reduces physical and earning capacity of the individual. Earliest documentation and probably one of first reports of aseptic necrosis of femoral head was reported by James Russel in the year 1794[(1)]. Two types of avascular necrosis are recognized. Traumatic where hip is the commonest location other sites being scaphoid, talus and proximal humerous. Non traumatic which usually occurs in young associated with alcohol, corticosteroids, decompression sickness, sickle cell disease, hemoglobinopathies, pregnancy, coagulopathies, inflammatory bowel disease, Systemic lupus erythematosus and sickle cell disease[(2)]. Various mechanisms have been postulated in the etiopathogenesis of this disorder like increase in intraosseous pressure resulting from lipocyte hypertrophy and derangements in fatty metabolism causes deposition of fat in the marrow spaces of the skeleton in patients who were treated with steroids particularly in the patients who received short term high steroids. In addition a correlation has been seen between glucocorticoids and bone death which appears to be due to blood stasis and ischemia in trabecular bone [(3)]

Radiography, CT scan, MRI scan and Digital substraction angiography are helpful in diagnosis and staging. It poses a great difficulty to treat patients with autoimmune diseases like pemphigus who are already having AVN. The use of corticosteroids becomes difficult due to risk of developing AVN in other hip joint. We report a case with AVN having pemphigus successfully treated with cyclophosphamide alone.

Case Report

A 52 year old male patient presented in our outpatient department in 2011 with history of blisters all over body including oral cavity since last 4 years. On taking history it was learnt that patient was a diagnosed case of Pemphigus vulgaris since 2007 and received oral prednisolone starting with 60 mg and tapered in due course of time in private setup. The lesions reappeared after decreasing the steroids and he was referred to a tertiary centre where he was prescribed oral steroids along with azathioprine in the dose of 50 mg daily. During the treatment in 2010 patient developed slight pain in left hip joint and difficulty in getting up from squatting position which he neglected. The pain increased gradually and he experienced difficulty in walking. On orthopedic evaluation the condition was diagnosed as a vascular necrosis of the head of the femur. MRI scan confirmed the evidence of AVN on right hip joint and early features of AVN on right hip joint. Oral steroids were tapered by the specialists in that tertiary centre and later on stopped. Patient was advised strict bed rest, along with non steroidal anti inflammatory drugs and total hip replacement. According to the patient the blisters reappeared within 2 months of stopping of steroids. There was no history of smoking, alcohol intake in the past. There was no history of tuberculosis, diabetes mellitus and hypertension before 2010. On examination there were approximately 30 to 35 vesicles and bullae all over body. (Figure 1) Oral cavity showed erosions in buccal mucosa. Genitals, palms, soles and eyes were not affected. At places bullae ruptured to form erosions with pus discharge at few places. General examination revealed no abnormality. Examination of left hip joint showed pain and limping during walking. Joint movements were restricted in all directions. These findings were of lesser severity on right hip joint. Systolic and diastolic blood pressures were 140 and 94 mm of mercury respectively. Clinical diagnosis of Pemphigus Vulgaris with Avascular necrosis of neck of femur with hypertension was kept. Routine investigations like blood count and erythrocyte sedimentation rate were normal. Fasting and post meal blood sugar were 150 and was 220 respectively. Liver and renal function test were within normal limits. Electrocardiogram showed no abnormality, X ray chest and ultrasonography of abdomen were within normal limits. Tzanck smear and histopathogical examination reconfirmed the diagnosis of Pemphigus Vulgaris.

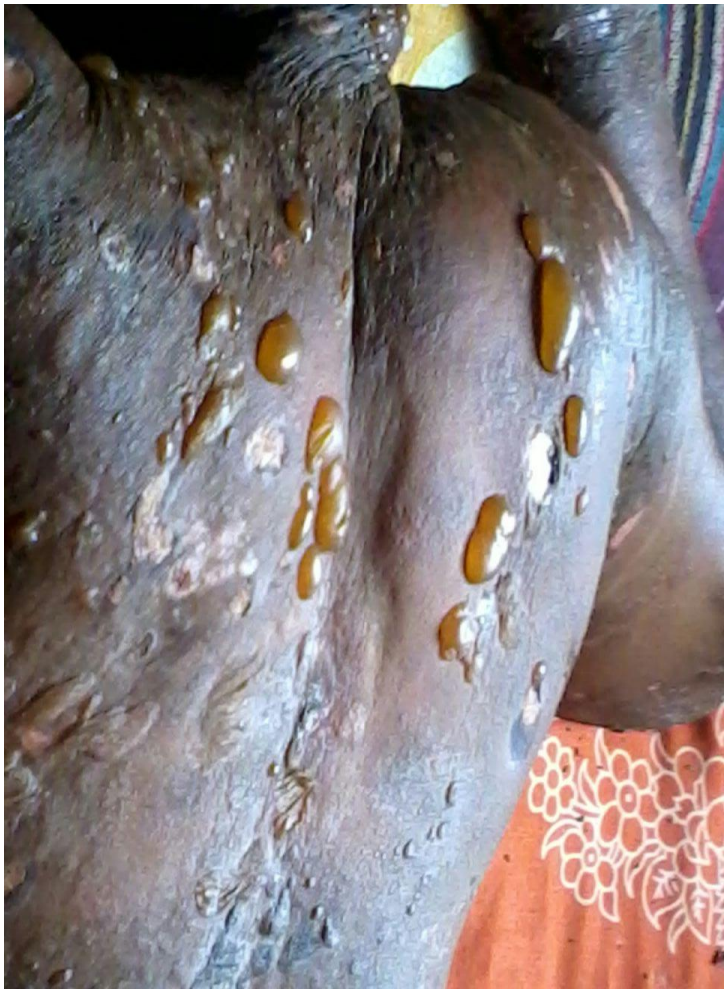

Fig 1: Pretreatment photograph showing blisters on back

Coronal T1 weighted image and ST1R images of MRI scan done in 2010 revealed hypointence region along with deformed shaft suggesting sclerosis and subchondral fracture on left femoral head. Diffuse hyperintensity in left femoral head and neck on S1LR images suggest edema. Mild to moderate synovial proliferation/effusion was also seen on left side. Periarticular soft tissue hyperintensity on ST1R images suggests inflammation.T 2 weighted MRI shows early involvement on right side with hypointence shadow suggesting edema and flattening of femoral head. These described findings were in favour of AVN of both femoral heads (Mitchell class A on right side and class C on left side). Patient was started on antibiotics for 3 days. The final diagnosis of Pemphigus vulgaris with steroid induced Avascular necrosis of head of the femur along with hypertension and diabetes mellitus was kept.

Patient was given injection cyclophosphamide 500 mg intravenously followed by oral cyclophosphamide 50 mg daily. Care was taken to maintain adequate hydration during and after intravenous cyclophosphamide. Oral antidiabetic and antihypertensive were started. There was little improvement after 25 days of treatment with new blisters still appearing on trunk. There were signs of secondary infection. Patient was again started on higher antibiotics for 3 days. All investigations including platelet count and urine cytology were repeated and were within normal limits. The cyclophosphamide pulse was repeated in the second month however daily oral cyclophosphamide was raised to 75 mg. Patient was advised to maintain adequate hydration. At the end of second month there was significant improvement in lesions. No new blisters appeared. Patient received one more cyclophosphamide pulses in 3 rd month and dose of oral cyclophosphamide was maintained at 75 mg daily. Patient was evaluated at the end of 3 months.

After receiving 3 pulses of injection cyclophosphamide (monthly) and 75 mg oral cyclophosphamide (daily) remission was achieved. Hence injection cyclophosphamide pulses were stopped and oral cyclophosphamide was reduced to 50 mg daily which was continued for further 9 months. From 13th month onward oral cyclophosphamide was reduced to 50 mg alternate day. This was continued for further 6 months. When no recurrence was observed oral cyclophosphamide was stopped after total of 18 months of treatment. The patient is being followed up for last 2 years and is free of new lesions without any treatment. (Figure 2) During the course of treatment routine investigations including urine examination for red blood cells were done on fortnightly basis for initial 3 months and on monthly basis for rest of the 15 months. X ray hip joints taken in 2015 showed deformed mushroom shaped femoral head on the left side. Both the joints showed sclerotic and lytic lesions along with osteoarthritis on femoral and acetabular side. (Figure 3)

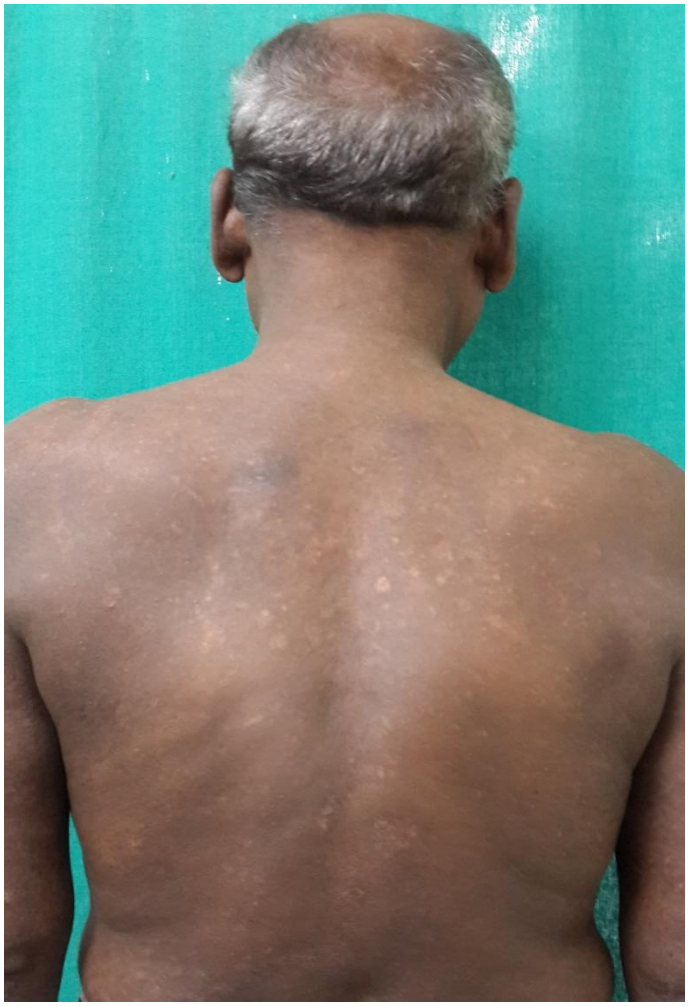

Fig 2 Post treatment photograph showing healing of blisters

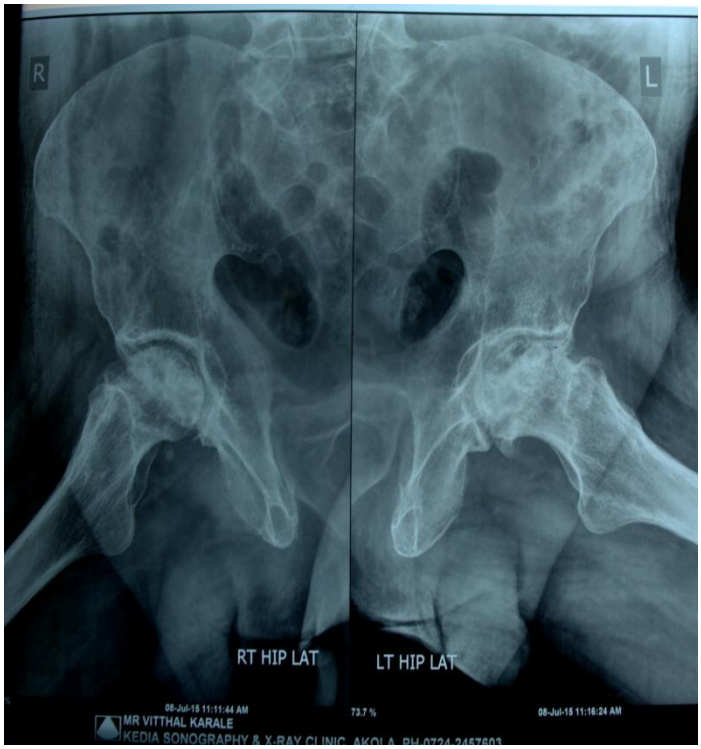

Figure 3 X ray shows showed sclerotic and lytic lesions along with osteoarthritis on femoral

Discussion

The use of corticosteroids has decreased the mortality in patients with vesiculo bullous disorders from 90 % to 15 % [(4)]. The duration of steroid treatment, the total cumulative and highest daily dose of steroids have been implicated as important factor in development of AVN[(3)]. In dermatological practice AVN has been reported more commonly with steroid use for SLE and less commonly in pemphigus[(5)]. Various authors have reported osteonecrosis of femoral head in patients receiving steroids[(3,5)]. 50% to 80% of patients with AVN in one joint develop AVN in other joint[(1)]. In such patients further use of steroids in treating pemphigus is debatable. In literature there are no such precedences described. To decrease the adverse effects steroids sparing drugs like cyclophosphamide, azathioprine and methotrexate have been used along with corticosteroid with varying success. Intravenous CYC has been used in treatment of several diseases including neuropsychiatric L E, Lupus nephritis, Wegeners Granulomatosis, Behcets disease and Granuloma pyogenicum. Mary E has reported good response in patients with Pemphigus by using CYC alone in pulse and daily oral treatment[(4)]. The use of CYC in pulse therapy has been shown to be quite efficacious but are associated with acute side effects like pancytopenia and haemorrhagic cystitis. Malignancies were reported with oral treatment which exposes the patient up to 2 mg/kg of CYC daily[(4)]. The cumulative dose when more than 36 grams leads to high risk of Acute Myeloid Leukemia and other malignancies like that of urinary bladder [(6)]. In our case CYC was given in 3 pulses to achieve remission along with oral CYC. It was continued on 50 mg daily for 6 months further and reduced to 50 mg alternate day. Thus total CYC received was 26 grams only as compared to approximately 44 grams given in conventional DCP. Urine analysis and cytology done every 3 months. Follow up was done since last 2 ½ year with no e/o relapse. It was noticed that AVN was quite obvious on left hip joint in 2010 and was in early stage on the right side. After 4 years even after avoiding steroids AVN has developed in the right hip joint as well.

Conclusion

As per our knowledge there is no reported case of Pemphigus Vulgaris with steroid induced AVN successfully treated with immune suppressive alone in the literature. This case report confirms the efficacy of cyclophosphamide in treating pemphigus as reported by others. It also highlights that if used with proper precautions oral cyclophosphamide can be used in higher doses for short period. This would decrease the dose of steroids required in phase 1 and consequently the duration of phase 1 in conventional DCP treatment advocated by Dr Pasricha. This case stresses the need of examination for signs and symptom's of AVN in every visit and periodic x rays of hip to detect AVN while prescribing high dose of steroids.

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