Case Report

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Cyclosporine -induced Kaposi Sarcoma; a Case Report of an Adolescent Male with Steroid-resistant Nephrotic Syndrome

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Although there are many reported cases of immunosuppressive-induced Kaposi sarcoma in renal transplant patients on immunosuppressive therapy, a similar report of Kaposi sarcoma among steroid-resistant nephrotic syndrome (SRNS) patients on immunosuppressive therapy is rare.
This is a report of a 12-year-old Nigerian adolescent male with SRNS who developed cutaneous Kaposi sarcoma following a prolong use of cyclosporine A. This case should serve as a reminder for the possibility of malignancy development, especially Kaposi sarcoma, when SRNS patients receive cyclosporine as a steroid-sparing immunosuppressive therapy.

Keywords: Steroid resistant nephrotic syndrome; cyclosporine A; Immunosuppression; Kaposi Sarcoma.

Running Title: Cyclosporine -induced Kaposi Sarcoma

Introduction

Kaposi sarcoma (KS) is a spindle shaped tumor of the endothelia origin [1,2]. KS usually involves the skin of the lower extremities, the head, and the trunk [2]. Other less commonly involved organs are the lymph nodes, lungs, liver, and gastrointestinal tract [2].
Nephrotic syndrome (NS) is a clinical glomerulopathy characterized by massive proteinuria (urinary protein excretion >40 mg/m^2/hr or urinary protein/creatinine ratio >2000 mg/g [>200 mg/mmol] or proteinuria >300 mg/dl or 3+ on urine dipstick) plus hypoalbuminemia (< 25g/l or 2.5g/dl) and edema [3]. NS is usually treated with corticosteroid therapy with >80% of the children achieving complete remission of proteinuria within 4 weeks of steroid therapy [4].

However, a subset of patients classified as steroid-resistant nephrotic syndrome (SRNS) may not achieve remission with corticosteroids [3, 4]. This group of patients is usually treated with steroid-sparing immunosuppressants like cyclosporine A [3-5]. While the development of KS in patients on long-term immunosuppressive therapy following renal transplantation is well-documented [6-8], the report of a similar association in a patient with NS is rare. The presented case is an adolescent Nigerian boy with SRNS who developed KS following treatment with cyclosporine A.

Case Report

BK, a 12-year-old boy presented to the Nephrology Unit of the Department of Pediatrics, University of Abuja Teaching Hospital (UATH),

Gwagwalada, Abuja, Nigeria with a history of progressive skin lesions that were first noticed about six months prior to presentation. The skin lesions were first described as few flat darkish rashes noticed initially on the left leg. The skin rashes, which were initially few in quantity and small in size, became nodular and increased in size, and spread to involve a wider part of the leg and the thigh. Similar progressive lesions were also noticed on the right leg after some time. The rashes were non-discharging and not excoriating, and there was no desquamation. There was no history of associated itching or pain and no history of similar rashes prior to administration of cyclosporine A.

Other presenting symptoms included a persistent fever, poor appetite, and a progressive weight loss, all of the same duration.

His past medical history revealed that he was diagnosed with SRNS at the age of 9 years following failure of remission of proteinuria to 12 weeks of prednisolone therapy at the referring hospital. A renal biopsy confirmed a focal segmental glomerulosclerosis, and cyclosporine A was started at a dose of 75mg twice daily plus a steroid every other day for 20 months. The child also received oral carvedilol, alpha calcidiol, calcium and magnesium supplements, iron tablets, and subcutaneous erythropoietin twice weekly.

At presentation, clinical examination of the musculoskeletal system revealed bilateral non-pitting pedal edema that extended up to the knee. There were multiple discrete purplish to dark nodules on both lower limbs. The largest one was located on the lower third of the left leg and measured 6 by 12 cm with an extensive surrounding area of hyperpigmentation (Figure 1).

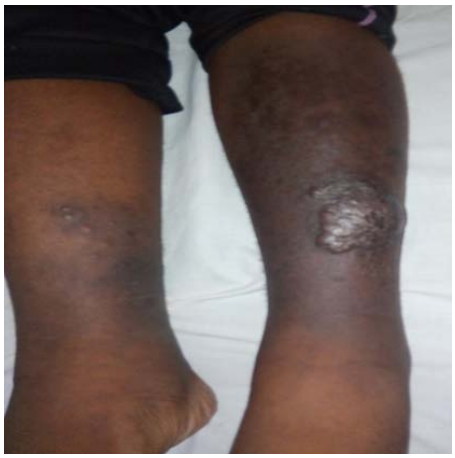

Figure 1. Nodular lesion with surrounding area of extensive hyperpigmentation and bilateral non-pitting pedal edema

There were also pallor, a non-tender inguinal lymphadenopathy, and a non-tender hepatosplenomegaly.

Laboratory findings included pancytopenia (total white blood cells: 2.9 X 10^9 cells/L, hemoglobin: 6 g/dl, platelet count: 73 X 109 cells/L), azotemia (serum urea: 22.9 mmol/L, serum creatinine: 413 µmol/L, estimated glomerular filtration rate: 23 ml/min/1.73m^2, serum bicarbonate: 23 mmol/L), massive proteinuria (spot urine protein /creatinine ratio: 1.081 mg/mmol), hypoalbuminemia (serum albumin: 25 mg/dl), hypertriglyceridemia (triglyceride: 9.79 mg/dl), and sterile pyuria. Hepatitis B and C, and HIV serology screening were negative. His hemoglobin electrophoresis was AA.

Radiological investigation showed features of bilateral renal parenchyma disease and multiple intrahepatic nodules on the abdomino-pelvic ultrasound, suggestive of an intra-hepatic KS visceral involvement (Figure 2).

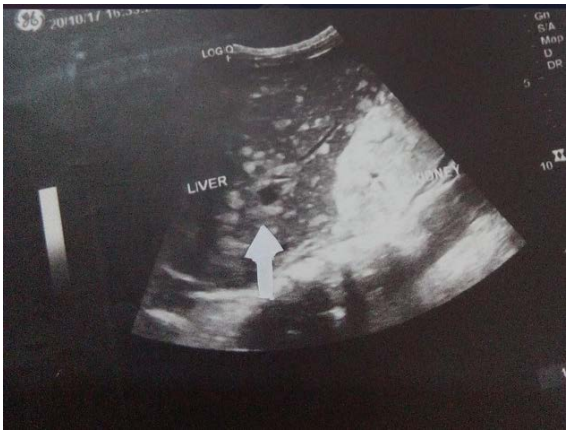

Figure 2. Ultrasound snap of the liver with an arrow pointing to one of the intrahepatic nodules

A skin biopsy of the right leg nodule was taken and sent for histology. The specimen was described as a tiny skin fragment measuring about 0.5 cm (AE). Histology revealed an orthokeratotic epidermis overlying a mesenchymal dermal neoplastic lesion (Figure 3). The lesion consisted of proliferating spindle cells with plump elongated nuclei (Figure 4) that were focally forming vascular slit-like channels with occasional red cells, hemosiderin laden macrophages, and hemosiderin deposits in the intercellular space disposed in a fibrocollagenous stroma (Figure 5). A diagnosis of early Kaposi sarcoma was made. Liver biopsy was not done.

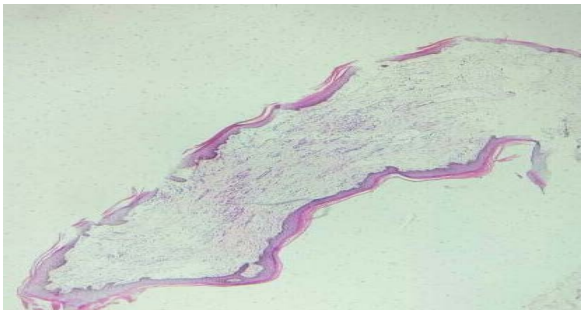

Figure 3. Orthokeratotic epidermis overlying a dermal lesion (H &E, X40)

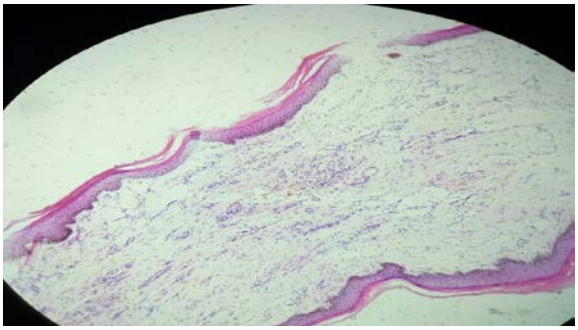

Figure 4. Proliferating neoplastic spindle cells having plump elongated nuclei (H & E, X100)

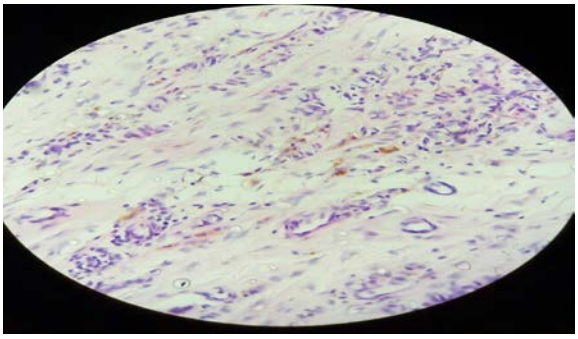

Figure 5. Slit-like vascular channels, red cells, hemosiderophages, hemosiderin deposits and stroma (H & E, X400)

Based on the above histological findings, a history of prolong immunosuppressive therapy, and clinical examination findings, the patient was diagnosed to have immunosuppressant-induced KS. Cyclosporine was discontinued and replaced with mycophenolate mofetil at a dose of 300 mg/m^2 surface area twice daily for massive proteinuria. The child is also visited by dermatologists.

Discussion

KS is a common malignant complication of prolonged immunosuppressive therapy, especially in renal transplant patients [6-8]. This association is thought to be due to the defective immune surveillance system in the patients as a result of inhibition of tumor suppressor gene p24 [9]. The risk of the development of KS following immunosuppressive therapy with cyclosporine A has also been observed to be higher than that of other immunosuppressive agents [8].

Cyclosporine A induces phenotypic changes, including invasiveness of non-transformed cells, by a cell-autonomous mechanism [9, 10]. Its use is associated with striking morphological alterations, including membrane ruffling and numerous pseudopodial protrusions, increased cell motility, and anchorage-independent invasive growth [10]. These changes are prevented by treatment with monoclonal antibodies directed at transforming growth factor-β (TGF-β) [10]. These findings suggest that immunosuppressive drugs like cyclosporine can promote cancer progression by a direct cellular effect that is independent of its effect on the host's immune cells, and that cyclosporine-induced TGF-β production may be involved in this pathogenesis [9, 10].

In some cases, withdrawal of the immunosuppressive therapy may result in complete resolution of the KS lesion [6, 8, 11]. Although the determinants of spontaneous regression are not known, however, mycophenolate has been shown to be effective in expediting Kaposi sarcoma regression [6, 8]. Furthermore, treatment of KS in renal transplant patients includes the use of proliferation signal inhibitors such as sirolimus and everolimus, which are also effective in the management of SRNS [6].

Conclusion

In conclusion, this case report showed the possibility of KS in SRNS following a prolonged exposure to cyclosporine A, a second line immunosuppressant recommended for treating SRNS [3]. It calls for a close dermatological examination whenever patients with SRNS are commenced on cyclosporine A, as early diagnosis of KS has been reported to portend a better prognosis [11]. Treatment of immunosuppressive induced-KS includes withdrawal of cyclosporine and replacement with an alternative immunosuppressant that is less likely to cause KS.

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Authorship contribution

All the authors participated in the design of study, acquisition of data, and interpretation of data. All the authors also participated in the initial draft of the article, and all authors revised it critically for important intellectual content. All the authors also gave approval of the version to be published. The requirements for authorship have been met by the authors.

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