



## IDIOPATHIC, TREATMENT RESISTANT, GIANT OESOPHAGEAL ULCER IN A KIDNEY TRANSPLANT RECIPIENT.

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**ABSTRACT** Giant oesophageal ulcers (GOU) are variable defined as ulcers larger than 10-20 millimeters. The initial reports were primarily in association with human immunodeficiency virus (HIV). Since then they have been described in the setting of organ transplant including hematopoietic stem cell and lung transplantation. Association with kidney transplantation is rare and only three such cases have been described. The pathophysiology remains an enigma. We report a case of idiopathic, therapy unresponsive, GOU in a young male with Immunoglobulin A nephropathy (IgAN) related end stage kidney disease. Four months following the kidney transplantation he presented with graft dysfunction, reoccurrence of basic disease, odynophagia and weight loss. The endoscopic evaluation showed two GOU in the distal esophagus. The response to therapy was poor; it finally resolved spontaneously. Based on the temporal profile and the review of existing similar case reports, we believe, these GOU represent an extra-renal manifestation of IgAN.

**KEYWORDS :** Kidney Transplant Recipient, Giant Oesophageal Ulcer, Iga Nephropathy.

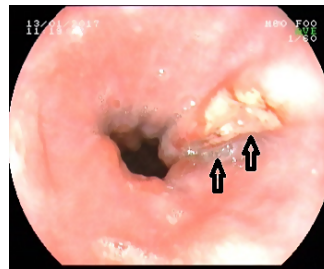
### INTRODUCTION

Amongst the various options for patients with end stage kidney disease (ESKD), kidney transplantation offers the best long-term outcome. Transplantation is associated with many complications. Gastrointestinal complications are frequent, and may be seen in up to 40% of kidney transplant recipients (1, 2). The gastrointestinal complications are usually mild and self-limiting; in few, it may be life-threatening. Giant oesophageal ulcer (GOU) is one such rare but sinister complication. It was first described in association with human immunodeficiency virus (HIV) (3, 4). Association with kidney transplantation is rare and till date, three such cases have been reported worldwide (5, 6, 7). We present a patient with IgAN related ESKD, who following the transplantation, developed idiopathic GOU.

### CASE STUDY

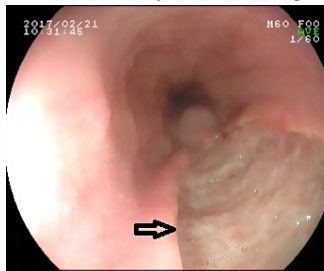
A 26 years old male was incidentally detected to have azotemia and proteinuria. The serum creatinine was 1.8 milligram/deciliter; urine analysis showed 2+ protein and numerous dysmorphic red blood cells. The 24 hours urinary protein was 1.1 gram. The tests for antinuclear antibodies, anti-neutrophilic cytoplasmic antibodies, hepatitis-B, hepatitis-C and HIV were negative. The serum complements were normal. The kidney biopsy was consistent with the diagnosis of IgAN and he was started on conservative management. Over the next two years he progressed to ESKD and hemodialysis was started. After being on hemodialysis for six months he underwent live related kidney transplantation. The donor was his human leucocyte antigen, haplo-identical, father. The induction therapy was with basiliximab and the maintenance immunosuppression included tacrolimus, mycophenolate and prednisolone. The immediate post-operative period was uneventful and he achieved a base line serum creatinine of 1.5 milligram/deciliter.

Four months following the transplantation, he developed unexplained graft dysfunction (serum creatinine: 2.0 milligram/deciliter). The graft kidney biopsy showed reoccurrence of IgAN. There were no histopathological features of rejection, tacrolimus toxicity, graft pyelonephritis or viral infection. The drug levels for tacrolimus were therapeutic. Two weeks later, he developed odynophagia. The examination of the oral cavity was normal. The total leucocyte counts were 2800/ cubic-millimeter; other laboratory parameters were normal. An upper gastrointestinal endoscopy (UGIE) showed gastroduodenitis and two linear 40-millimeter ulcers in the distal esophagus (Figure 1). The rapid urease test was negative and a biopsy taken from the ulcer bed showed mixed inflammatory infiltrate. The polymerase chain reaction (PCR) for BK virus, cytomegalovirus (CMV) and herpes simplex virus (HSV) 1 and 2 were negative.



**Figure 1: Endoscopic image of the distal esophagus showing two giant oesophageal ulcers (arrow heads)**

There was no response to withdrawal of mycophenolate and increase in the dose of steroids. With a strong clinical suspicion of CMV related oesophageal ulcer, oral valganciclovir was started. The symptoms persisted despite 2 weeks of therapy. A repeat UGIE showed an increase in the size of GOU. His oral intake was meagre and he had lost 16 kilos weight. Oral valganciclovir was stopped; intravenous ganciclovir and oral acyclovir were started, as an empiric cover for both CMV and HSV. The symptoms however persisted. A repeat UGIE showed, the two oesophageal ulcers have coalesced (Figure 2). At this juncture, all medications except tacrolimus and prednisolone were withdrawn. Over the next 8 to 12 weeks, his symptoms gradually improved. Subsequent followup showed, progressive worsening of kidney function over the next one year, culminating in ESKD.



**Figure 2: Follow up UGIE showing a coalesced, giant oesophageal ulcers (arrow head).**

### DISCUSSION

IgAN is the commonest primary glomerulopathy worldwide. The disease spectrum varies from asymptomatic hematuria to rapidly progressive renal failure. The initiation of disease is attributed to a

'multi hit process'; the common thread being presence of circulating and glomerular immune complexes comprising of galactose-deficient IgA1, an IgG autoantibody directed against the hinge region O-glycans, and C3.

Oesophageal ulcer is defined by the loss of mucosal continuity. In the background of transplantation, the differential diagnosis includes infection, gastro-oesophageal reflux, neoplasm, drugs and systemic diseases. Infections are the most common cause, with candida, CMV and HSV accounting for the majority. Amongst medications, up to one-third of patients on mycophenolate have gastrointestinal symptoms and around 5% may develop esophagitis and gastritis. An idiopathic GOU is a diagnosis of exclusion. The initial reports were primarily in association with HIV (3, 4). Since then they have also been described in the setting of organ transplant including hematopoietic stem cell and lung transplant (8, 9). Association with kidney transplant is rare and only three cases have been described worldwide (5, 6, 7). We intend to discuss these three cases along with our case so as to derive common pattern.

The first reported case of GOU was a 31 years old man with IgAN related ESKD who presented four months post-transplant with severe odynophagia and weight loss (5). There was a history of recent rejection. The maintenance immunosuppression included cyclosporine, mycophenolate and prednisolone. The endoscopy showed 30-millimeter distal oesophageal ulcer with inflammatory changes on biopsy. The response to oral acyclovir and clotrimazole was poor. The markers for CMV, HSV and adenovirus were negative. The patient eventually responded to an increase in the dose of steroids. The author hypothesized that the GOU is a consequence of defect in T lymphocyte function.

The second reported case was of a 45 years old male with IgAN related ESKD who developed a 20-millimeter distal oesophageal ulcer six months following the transplant (6). The induction was with rituximab; the maintenance immunosuppression was similar to the first case. He presented with odynophagia and weight loss. Leucopenia was observed; the biopsy did not provide any additional clue. The markers for CMV, HSV and HIV were negative. There was no response to discontinuation of mycophenolate. He responded to an increase in the dose of steroids. The authors hypothesized the etiology to be rituximab related.

The third case was of a 37 years old female who presented six months following kidney transplantation with odynophagia, epigastric pain, weight loss and leucopenia (7). The maintenance immunosuppression was similar. UGIE showed 40-millimeter distal oesophageal ulcer with biopsy showing acute inflammatory changes and presence of candida species. The serological markers for CMV, HSV and adenovirus were negative. There was no response to fluconazole and discontinuation of mycophenolate. She responded dramatically to intravenous acyclovir. The authors hypothesized, immune imbalance to be the etiology.

On analyzing these cases, a common pattern emerges. GOU occurs in the early post-transplantation period in young subset of patients with IgAN. The manifestations include odynophagia, weight loss, leucopenia and distal oesophageal ulceration with biopsy showing non-specific inflammatory changes. A therapeutic response was noted to steroids in the first-two cases, to acyclovir in the third case, while our patient did not respond to any of these. As reduction of immunosuppression was one of the interventions which lead to resolution of the pathology, all the authors hypothesized immune-imbalance as the likely etiology. Looking objectively, multiple sequential interventions were attempted in these rapidly deteriorating patients, and as to which intervention lead to resolution is debatable.

We tend to disagree with existing hypothesis based on following. A large number of patients undergo kidney transplantation and are on regular close followup. A significant proportion of these have IgAN. We also know, that the net immunosuppression cannot be objectively measured and hence it is safe to assume that some will be under-immunosuppressed, some over-immunosuppressed and some optimally-immunosuppressed. The under-immunosuppressed cohort have a higher likelihood of manifesting as graft rejection and hence their proportion is likely to be low. We can hence safely conclude, that at any given time there is a large cohort of patients with IgAN who have undergone kidney transplantation, who are either optimally or over-immunosuppressed. If the hypothesis of immune imbalance would

have been true, there would have had been many more cases of GOU worldwide and not the occasional case-reports. This is especially so as the presentation is so dramatic and disabling.

We propose an alternative hypothesis. The common thread binding all these patients is the presence of IgAN. IgA, while playing a major role in the pathogenesis of IgAN also plays a vital role in the mucosal immunity. We feel, this aberrant IgA has an important role in the pathogenesis of GOU. In our patient we noted a temporal relationship between, reoccurrence of IgAN, graft dysfunction, and onset of GOU. As to why only few patients develop GOU, we feel, that this extra-renal manifestation of IgAN is a multihit process. The second hit could be viruses both known and unknown, cryptic antigens or an environmental factor superimposed on genetic predisposition. Regarding the reason for steroid responsiveness in the first two cases, we feel, the steroid responsiveness of oesophageal ulcer is akin to renal response in proteinuric IgAN; some respond and some do not.

## CONCLUSIONS

Idiopathic GOU is a rare, disabling, complication which occurs on the background of IgAN in the early post transplantation period. It preferentially affects, younger subset of patients. The presentation includes odynophagia and weight loss. It is a diagnosis of exclusion. The various therapeutic options that have been attempted include steroids, acyclovir and or ganciclovir along with reduction in immunosuppression. We hypothesize that these GOU represent an extra-renal manifestation of misdirected galactose deficient IgA.

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