Association of IgA Nephropathy with Squamous Cell Carcinoma of the Tongue: – Case Report and Review of Literature

Abstract

A 32-year-old habitual tobacco chewer was diagnosed with squamous cell carcinoma of the tongue. He was initiated on chemo-radiation therapy. After completing 23 cycles of radiation and four cycles of cisplatin-based chemotherapy, he presented with acute nephritic syndrome. Renal biopsy showed IgA nephropathy and acute tubular injury. With supportive care, renal function stabilised with a reduction in proteinuria. We wish to highlight the poorly understood association between mucosal malignancies and IgA nephropathy. It is also interesting to note the peculiar temporal profile of glomerular involvement in our patient, where the onset of the glomerulonephritis was after the initiation of chemo-radiotherapy. This is unlike what has been described earlier.

Keywords: *Chemo-radiotherapy, IgA Nephropathy, mucosal malignancy, tongue carcinoma*

Harshavardhan T Sanathkumar, K Thirumalvalavan, T Yashwanth Raj, ND Srinivasaprasad, S Sujith, Edwin M Fernando

Department of Nephrology, Govt Stanley Medical College and Hospital, Chennai, Tamil Nadu, India

Introduction

IgA nephropathy associated with systemic diseases is a rare and poorly understood entity. The association of IgA Nephropathy with malignancy is uncommon. We wish to highlight one such case of IgA nephropathy associated with tongue malignancy, which is rare in itself; in addition to a peculiar temporal profile in our patient.

Case History

A 32-year-old male had presented to the general surgical unit of our hospital with complaints of swelling over the left side of the tongue associated with pain for 8 months. He was a habitual tobacco chewer. On assessment, he was found to have a 5 cm × 3 cm ulcero-proliferative growth on the dorsal aspect of the left side of the tongue, extending from its tip to the level of the second molar posteriorly. Retromolar area, the base of tongue and floor of mouth were not involved macroscopically. Biopsy of the lesion was suggestive of moderately differentiated squamous cell carcinoma. MRI of the neck revealed malignancy confined to the tongue with no discernible secondaries or lymphadenopathy. His creatinine documented at that time was 1.2 mg/dL with normal urine analysis.

In consultation with medical oncology, the patient had been initiated on chemo-radiotherapy. He was given four cycles of weekly Cisplatin. Simultaneously, radiotherapy (brachytherapy) was initiated at a frequency of five sessions per week for 4 weeks. He subsequently presented to us with complaints of macroscopic haematuria and decrease in urine output for three days. At presentation, he had a blood pressure of 160/90 mmHg (right upper limb) with no pedal oedema. Post-radiation discolouration of the neck and face was noted [Figure 1]. The primary lesion in the tongue had marginally reduced in size (3.5 × 1.8 cm). There was no clinical focus of infection in the buccal mucosa or elsewhere. His creatinine was 3.4 mg/dL with urinalysis revealing microscopic haematuria (3+) and albuminuria (3+) on the dipstick. Urine microscopy revealed red cell casts. Quantification of urine protein was 1935 mg of protein excretion per day. Serum complement levels were normal. A diagnosis of the acute nephritic syndrome was made, and he was subjected to a renal biopsy. Cisplatin toxicity was also considered initially, but the presence of gross haematuria, proteinuria and RBC casts led us to suspect a glomerular pathology.

One biopsy core was analysed by immunofluorescence and was positive for

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Address for correspondence:
Dr. Thirumalvalavan K, Department of Nephrology, Govt Stanley Medical College and Hospital, No. 1, Old Jail Rd, Old Washermanpet, Chennai, Tamil Nadu - 600 001, India. E-mail: thirumalvalavan97@gmail.com

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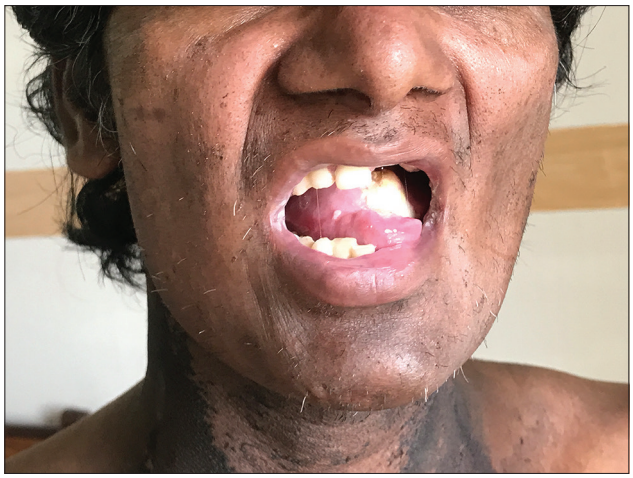

Figure 1: Patient with a malignant lesion in the dorsum of the tongue. Skin changes of radiation are conspicuous (discolouration, sparse hair, dry skin)

Immunoglobulin A (3+) and C3 (1+) in the mesangium. The other core was stained with Hematoxylin & Eosin in addition to special stains including Periodic acid Schiff, silver and trichrome. 19 glomeruli were seen on the biopsy, with four being globally sclerotic. Increase in mesangial cellularity and matrix expansion was noted. There were no foci of segmental sclerosis, endocapillary proliferation, crescents or necrotising lesions noted on the biopsy. The biopsy was scored as M1 E0 S0 T0 by the Oxford classification. There was tubular cell injury with RBC casts noted in the tubules. A diagnosis of IgA nephropathy associated with mucosal malignancy (Squamous cell carcinoma of the tongue) was made. There was no evidence of chronic liver disease on imaging or biochemical evaluation.

With conservative measures, creatinine settled to 1.4 mg/dl. He was initiated on anti-proteinuric measures and advised to continue therapy for his tongue malignancy. At 1-year follow-up, his tumour has regressed in size, but he persists to have microscopic haematuria with proteinuria having reduced to less than 500 mg per day with normal renal function.

Discussion

Secondary IgA Nephropathy

IgA nephropathy (IgAN) is the most common primary glomerulonephritis in the world. Secondary IgAN is relatively rare and has been associated with liver disease (alcoholic cirrhosis, non-alcoholic steatohepatitis), gastrointestinal disease (celiac disease, Crohn's disease), malignancy (renal cell carcinoma, bronchial malignancy, laryngeal carcinoma, lymphoma), chronic infections (HIV, hepatitis B, C) and some auto-immune diseases.[1] The true incidence of secondary IgA is difficult to estimate, but chronic liver disease is the most common underlying cause. An analysis of studies/reports since 2000 in the PubMed database revealed at least 50 separate diseases and pathogens that have been linked with the development of IgAN. Some of these case reports, however, may reflect a chance association because the occurrence of subclinical IgA is quite high in the general population.[2]

Malignancy & IgA – An association or chance?

Malignancy associated IgAN was first systematically investigated by *Mustonen* in his seminal paper on this subject in 1984. Out of a total of 184 cases of IgAN over a 7-year period, six cases (3%) were associated with malignancy. In two of these patients (tongue and pancreatic malignancy), the glomerular pathology pre-dated the clinical diagnosis of malignancy by more than 2 years. In the other four cases (Bronchial, nasopharyngeal carcinoma, retroperitoneal sarcoma), the diagnosis of both malignancy and IgAN was concurrent.[3] Since then, IgAN has been described in patients with gastric malignancies, renal cell carcinoma, lymphomas and myeloma. A recent report demonstrated that the clinical presentation of IgAN led to the detection of recurrent adenocarcinoma of the stomach.[4] The association of renal cell carcinoma and IgAN deserves a special mention as the association has been well demonstrated. In a study from Hungary, renal tissue found in excised specimens of renal cell carcinoma were studied; 18% of these patients had features of IgAN. It was noted that in 54% of them, pre-operative proteinuria and hematuria regressed within 3 months of surgical excision of the tumour. Adult-onset Henoch–Schonlein purpura has also been associated with various solid organ and haematological malignancies. Such demonstrations, along with clustering of disease association with certain types of malignancies (especially mucosal and renal) suggest that this link is not merely coincidental, but paraneoplastic features, that occur due to immunological mechanisms that are yet to be elucidated.[5]

Primary oral and laryngeal cancer patients have been shown to have a two-fold increase in serum and salivary IgA compared to controls.[6] It is unclear whether this is due to chronic mucosal irritation by the malignant cells or a response to specific tumour antigens. It is also possible that both the malignancy and the glomerular disease are expressions of an altered immune response to common inciting antigens.[1,3,7]

Tongue malignancy and IgAN– Atypical temporal profile in our patient

There has only been one other case of tongue malignancy associated with IgAN reported in literature, that we could find. In that case, the glomerular disease preceded the clinical onset of malignancy by 2 years. It is important to point out that the association in our case is not an incidental deposition of IgA on the kidney biopsy, rather a patient who was symptomatic with the syndrome of acute nephritis and diagnosed with IgAN that makes this association worth reporting.

In addition to the rarity of this association, the peculiarity in our patient was that the glomerulonephritis presented when the patient had begun therapy (radiation and chemotherapy), and the primary tumour had started to shrink in size. Some prior case reports have suggested regression of proteinuria and/or renal symptoms with therapy or excision of the tumour. Others have reported persistence of the glomerular syndrome despite the regression of the primary tumour. None have highlighted the onset of disease after chemo-radiation for the tumour. It is possible that chemo-radiation could have modulated local mucosal factors to increase expression or release of pathogenic IgA molecules by the tumour cells undergoing destruction. It is also possible that the lytic tumour cells or chemo-radiation induced mucosal damage per se induced an aberrant immune response, triggering abnormal IgA production.[8] We felt that this unique temporal profile deserved mention as it could throw light on the underlying pathogenic mechanism for this association of mucosal malignancy and IgAN, which needs further elucidation. We were able to find one other case report of an elderly patient with prostate malignancy, undergoing brachy-radiotherapy. He had subsequently presented with rapidly progressive glomerulonephritis and was diagnosed to have proliferative and crescentic IgAN.[8,9]

Mucosal-glomerular cross-talk – Avenues for research

The association of IgAN with mucosal pathologies like chronic inflammatory bowel diseases (celiac disease, inflammatory bowel disease), chronic lung pathologies (chronic obstructive bronchiolitis, idiopathic pulmonary fibrosis, cystic fibrosis), gastrointestinal, buccal, bronchial malignancies and more commonly, mucosal infections, establishes the presence of the mucosal-glomerular cross talk. This is strengthened by the fact that the mesangial IgA deposits are usually polymeric which is likely to be of mucosal origin (mucosal IgA is the secretory type and polymeric). Our case report further adds to the body of evidence of this cross-talk. The exact pathogenic mechanisms and the missing links in this cross-talk are avenues of research that need more focus.[1,10]

Conclusion

In clinical practice, IgAN is usually considered a primary glomerular pathology, and we often do not seek to evaluate for other secondary causes. It is considered prudent to evaluate for secondary causes, especially, malignancy, in patients being diagnosed with IgAN after 60 years of age. In patients with IgAN and risk factors for neoplasia (e.g., smokers, tobacco chewers, prior gastrointestinal or lung malignancy), it may be worthwhile to entertain a focused evaluation, even in the young.[11]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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