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PARANEOPLASTIC SYNDROMES IN PATIENTS WITH ORAL CANCER

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ABSTRACT

Paraneoplastic syndromes (PNS) include a series of disorders that accompany benign and malignant tumors. PNS occurs in one to seven percent of all cancer patients, however the evidences seem to be increasing. PNS associated with head and neck cancer can be divided into six main groups : endocrine, cutaneous or dermatologic, hematologic, osteoarticular or rheumatologic, neurologic and ocular syndromes. PNS can precede, follow or be concurrent with the malignant tumours. The following review thus aims to highlight various aspects of different Paraneoplastic syndromes and how important is awareness of these conditions for clinicians dealing with cancer.

KEYWORDS: Oral cancer, Paraneoplastic syndrome. Early detection, Head and neck cancer.

INTRODUCTION

Paraneoplastic syndrome is a disease or symptom that is the consequence of presence of cancer in the body, but is not due to the local presence of cancer cells[1]. Oral cancer is the sixth most common human malignancy globally, however in India it ranks third. Globally, about 500000 new oral and pharyngeal cancers are diagnosed annually. There is an increasing evidence that PNS occurs in association with oral cancer. We have reviewed the literature in order to investigate the various PNS related to oral cancer and their relevance to the diagnosis.

Paraneoplastic Syndromes(PNS)

PNS occurs in 1-7 % of all cancer patients. The pathophysiology of most PNS is not well known, PNS can precede, follow or be concurrent with the malignant tumour. The exact incidence of PNS associated with any cancer is difficult to determine, because of numerous "false-PNS" cases reported so far.Amongst all the paraneoplastic syndromes reported till date,endocrine and the dermatologic syndromes have been found to be mostly associated with oral cancer.

Paraneoplastic Endocrine Syndromes and Oral Cancer

Syndrome of inappropriate secretion of Antidiuretic hormone (SIADH): The usual mechanism of development of paraneoplastic endocrine syndromes is the aberrant production of protein hormones, hormone precursors or hormone like substances by tumour tissue. Among head and neck tumours, paraneoplastic SIADH is most commonly associated with squammous cell oral cavity cancer. 2 retrospective studies reported an incidence of 2% in a series of 260 cases and an incidence of 3% in 1436 patients respectively.

In 1987, Okutomi et al reported a case of squamous cell carcinoma of the tongue and floor of the mouth that had metastatized to the neck who had SIADH with an elevated serum antidiuretic hormone.

In the initial report of SIADH associated with bronchogenic carcinoma, it was hypothesized that the cause of PNS was ectopic secretion of argenine vasopressin[1,2].

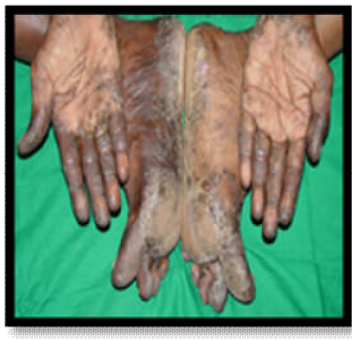

Fig.1.Psoriasiform skin lesions as seen in Bazex syndrome.

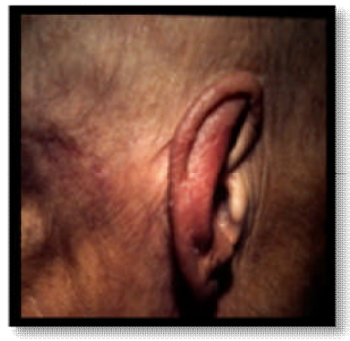

Fig.2.Cutaneous manifestations in Bazex syndrome.

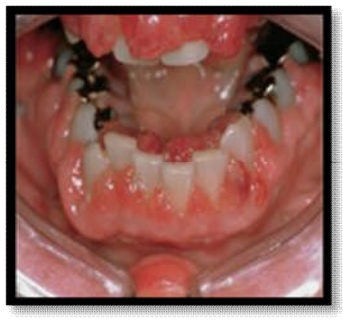

Fig.3.Oral manifestations in sweet syndrome.

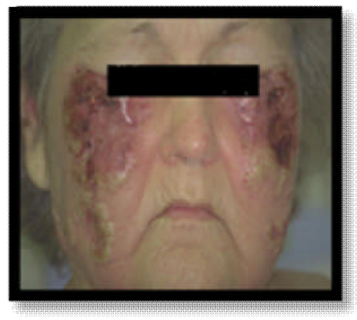

Fig.4.Erythematousnodules and plaques on the skin as seen in sweet syndrome.

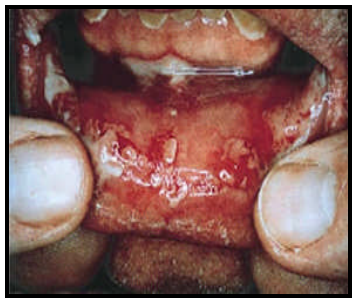

Fig.5.Maculopapular rash seen in paraneoplastic pemphigus.

Fig.6. Dermatologic PNS may be a premonitory sign towards an oral tumour

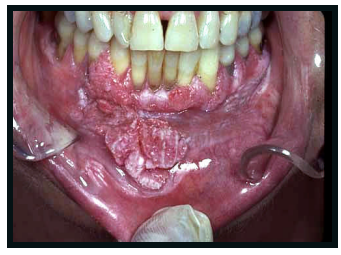

Fig.7. Malignancy in association with a paraneolastic syndrome.

Paraneoplastic Cutaneous or Dermatologic Syndromes and Oral Cancer

The appearance of skin lesions in patients with occult or obvious malignancy is of value in the detection and management of cancer because the skin is readily accessible to examination and biopsy.

Skin may be involved in systemic malignancies in five different ways:

1. Secondary spread (metastases).
2. Genetic disorder with a cutaneous component in which there is an inherited predisposition to the later development of malignancy (genodermatoses).
3. As a part of an acquired syndrome due to the toxicity of a carcinogen that induces malignant change and accompanying cutaneous changes.
4. As a consequence of immunosuppression, or
5. By the development of specific lesions that occur as PNS[1].

Acrokeratosis Paraneoplastica

Acrokeratosis paraneoplastica associated with a SCC of the tongue was first described by Gougerot and Grupper in 1922, whereas the name was given in 1965 by Bazex. Bazex syndrome was first described as a paraneoplastic process associated with a carcinoma of the pyriform sinus.

This syndrome is typically associated with malignancies of the upper respiratory or digestive tract. Usually, the cutaneous signs appear at the same time as the underlying tumor. Detection and recognition of this syndrome provide the opportunity to discover a malignancy at an early presymptomatic stage. The pathogenesis of Bazex syndrome remains to be determined. This is possibly initiated and triggered by a common antigen between tumor cells (usually SCC) and epidermal cells.

Another explanation for the psoriasiform skin(**Fig.1,2**) lesions in Bazex syndrome is based on the stimulating effect of transforming growth factor alpha produced by the tumor cells.

The treatment of the skin lesions is directly related to the eradication of the underlying neoplasm by surgery, chemotherapy or radiotherapy. Classically, the cutaneous manifestations disappearduring the treatment of the tumor[3,4].

Sweet Syndrome (Acute Febrile Neutrophilic Dermatosis)

Sweet syndrome may occur as a cutaneous PNS. Clinically it is characterized by the sudden appearance of multiple erythematousnodules and plaques on the skin(**Fig. 4**), leucocytosis and fever. It was first reported in 1964[2].

Paraneoplastic Pemphigus

The concept of paraneoplastic pemphigus was first described in 1990 by Anhalt et al. with the report of a distinct variant within the pemphigus spectrum associated with underlying neoplasms; mainly lymphoreticular malignancies. This variant is characterized by atypical, erythema multiforme-like clinical and histopathological features and the presence of antiepithelial IgG-type antibodies.

In approximately one-third of paraneoplastic pemphigus cases, no neoplastic lesions have been manifested at the time of development of mucocutaneous disease Van der Waal et al. reported a case of paraneoplastic pemphigus(**Fig.5**) that preceded the discovery of a non-Hodgkin lymphoma of the tongue by 16 months[1].

CONCLUSION

Two types of PNS have been reported in association with oral cancer; endocrine and dermatologic. The syndromes often vary in severity proportional to the extent of disease, and may be indicators of control or recurrence. A number of dermatologic conditions including Acrokeratosis paraneoplastica (Bazex syndrome), Acute febrile neutrophilic dermatosis (Sweet syndrome), paraneoplastic pemphigus and orofacial granulomatosis have been reported in association with oral cancer. Many of the dermatologic PNS may precede the clinical diagnosis of oral cancer by significant periods of time, and may be of help in anticipating the diagnosis. PNS are systemic and non-metastatic manifestations associated with a variety of malignancies. They produce signs and symptoms remote from the site of a malignant tumor, resulting from damage to organs or tissues by mechanisms that are not fully understood.

The exact frequency of PNS in patients with oral cancer is not known. Overlapping or incoherence of anatomical specification is due to different methods of reporting data that have been published in the literature. However, it is

quite possible that PNS occur more frequently in these patients than is generally recognized. Dermatologic PNS are less common, but may be a premonitory sign(**Fig.6**), as they frequently precede the oral tumor. Awareness of this association is important as the first indicator of a malignant tumor(**Fig.7**) or its recurrence.

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