Case Report

Metastasis in the mandible involving gingiva: An intriguing case with a perplexing pathology

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Abstract

Oral metastasis, although rare, tends to involve jawbones, particularly the posterior region of the mandible, and involvement of oral soft tissues, even when less likely, is most often seen on the gingiva and tongue. Clinically, the soft-tissue masses tend to mimic pyogenic granuloma, peripheral giant cell granuloma or an epulis and thus are difficult to diagnose and identify. The jaw bone is preferred by prostate carcinoma as a metastatic target. Prostate malignancy, which is more common in Western countries than in India, may be adenocarcinomas or carcinomas. Oftentimes, metastatic lesions develop in the alveolar region and are a cause for tooth mobility, yet, they tend to be detected only after extraction of the affected tooth. In such cases, the symptomatic presentation therefore, is vague and indicative of tooth mobility secondary to periodontal pathology unless, a detailed history and follow-up is done. We report a case of a male patient who presented to our department with a proliferative, painful, swelling postextraction of the left first molar region, and the lesion was seen at the extraction site as well as in the mandibular anterior tooth region. The swelling was associated with palpable lymph nodes. Orthopantomogram showed an irregular, radiolucent lesion extending from the lower left central incisor to the left first molar region in the mandibular alveolus. Incisional biopsy tissue came with provisional diagnosis of osteomyelitis or squamous cell carcinoma as the patient was a habitual bidi smoker for more than 20 years. Histologically, it was an undifferentiated tumor with tumor cells seen in deep connective tissue with a lack of lineage differentiation. An undifferentiated malignant tumor represents either a metastasis of unknown origin or a primary neoplasia without obvious cell line of differentiation. Immunohistochemistry (IHC) of undifferentiated tumors helps to categorize them into small round blue cell tumors or large cell tumors. The oral pathologist was perplexed as there was no mention of any other malignancy in the patient's history, which, however, was noted by the surgeons few days later. Hence, initially, a hematopoietic malignancy was suspected which was ruled out by IHC, and later, staining with cytokeratin 7 (CK7), CK-high molecular weight and P63 confirmed prostate metastases as all three were negative.

Keywords: Cytokeratin-7, cytokeratin-high molecular weight, metastases, numb chin syndrome, P63, prostate adenocarcinoma, undifferentiated tumor

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INTRODUCTION

The detachment of tumor cells from primary tumors with their subsequent emigration through the blood, lymph or serosal surfaces is a process supported by numerous biomolecules acting in a synchronized fashion and resulting after a complex biological course in metastasis.

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Most oral metastases involve jawbones, and mandible is the more common site of metastasis. Among the soft tissues of the oral cavity, although rare, involvement is mostly of the gingiva and tongue.[1]

From among the orofacial cancers, both, those located in the soft tissues of the oral cavity and in the jaws, only about 1% cancers are a metastasis of the primary tumors located elsewhere in the body. The diagnostic challenge begins, from their clinical aspects owing to the extreme similarity of clinical presentation of these lesions, particularly soft-tissue metastasis, with lesions such as pyogenic granuloma, peripheral giant cell granuloma or an epulis. Thus, they are difficult to diagnose and identify.[1,2]

Worldwide, the second most common cancer is prostate cancer, and it is also the sixth leading cause of cancer-related death among men. In India, the incidence of prostate cancer is lower in comparison with the same for Western countries. Prostate as the primary site for jaw metastasis is an extremely rare occurrence; still, the jaw bone is preferred by prostate carcinoma as a metastatic target because of its significant red marrow component. For example, as noted in some previous studies, among the jawbone metastasis in men, only 11% originated from the prostate gland and only 1.5% of soft-tissue metastases originated from the prostate gland. The most common location for metastatic jaw lesions is the molar region of the mandible. Histologically, prostate malignancies are common of either of the two types:

1. Adenocarcinoma arising from glandular acini and peripheral secondary ducts
2. Carcinoma of large primary ducts.

The primary malignant lesions that commonly tend to metastasize are primaries located in the breast, adrenal gland, genital organs, thyroid gland, lung, prostate and kidney. The sites of primary tumors in men in order of their incidence as reported in the literature are lungs (22.3%), prostate (12%), kidney (10.3%), bone (9.2%) and adrenals (9.2%).[2,3]

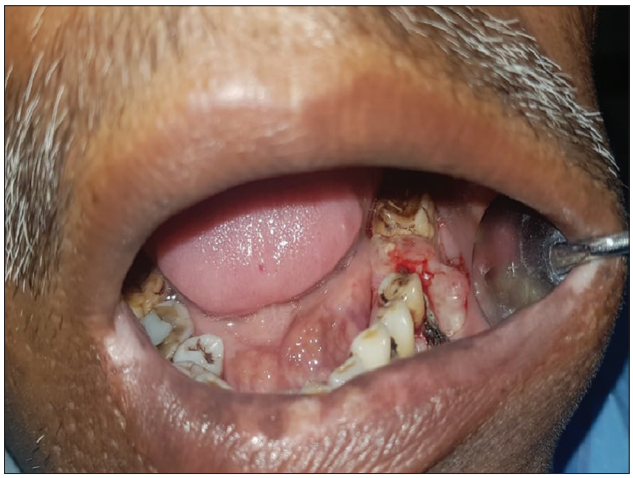

Figure 1: Clinical photograph of I. O lesions

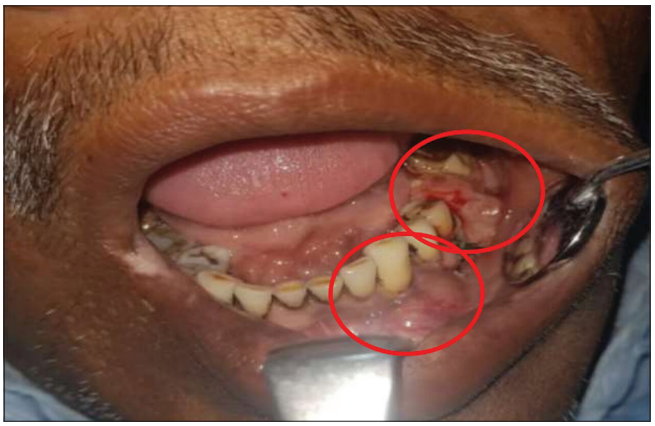

Figure 2: Clinical photograph of I. O lesions

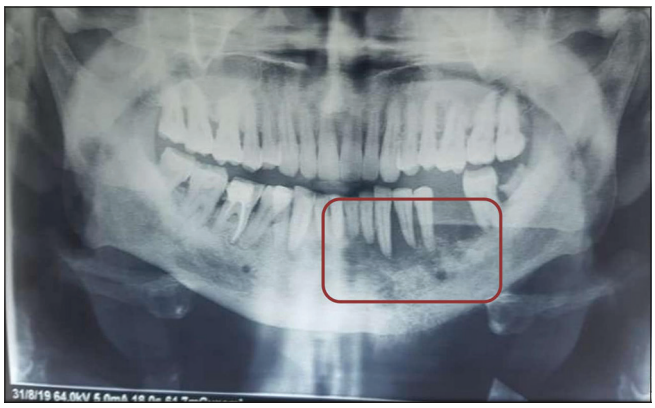

Figure 3: Orthopantomogram of the patient showing patchy radiolucency with irregular margins in the left anterior region extending as poorly defined radiolucency into the body of mandible region

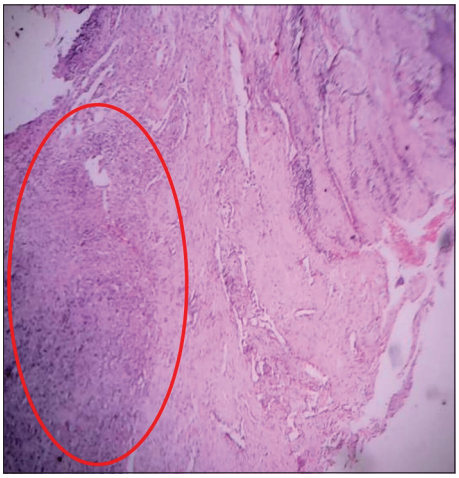

Figure 4: H & E stained sections in ×5 magnification showing diffuse presence of round cells in deep connective tissue

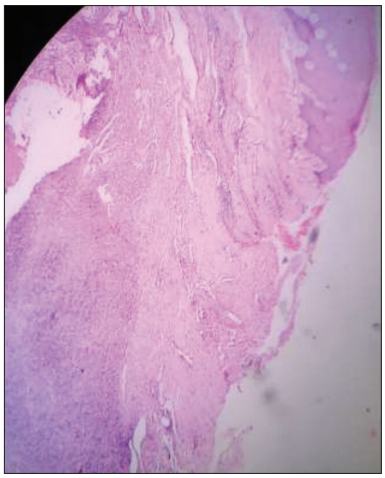

Figure 5: H & E stained sections in ×5 magnification showing diffuse presence of round cells in deep connective tissue

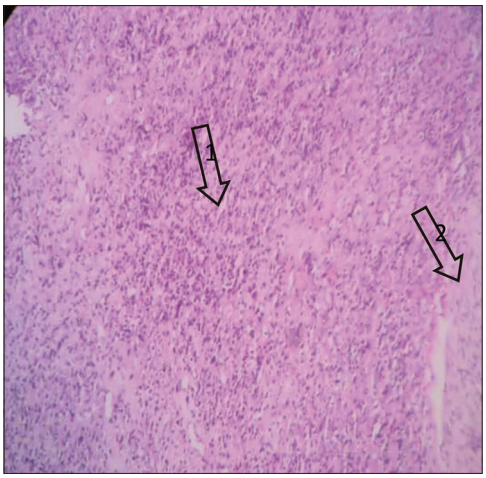

Figure 6: H & E stained sections in ×10 magnification showing diffuse presence of two different morphologies of cell populations in deep connective tissue

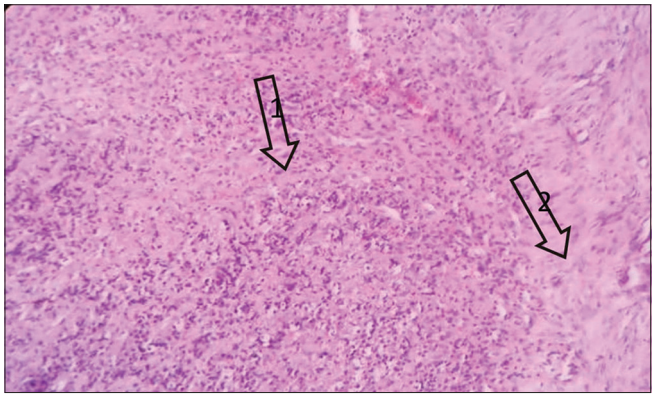

Figure 7: H & E stained sections in ×10 magnification showing diffuse presence of two different morphologies of cell populations in deep connective tissue

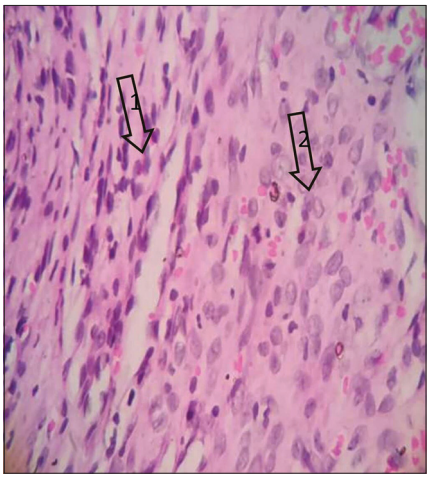

Figure 8: H & E stained sections in ×40 magnification showing diffuse presence of two different morphologies of cell populations in deep connective tissue

Metastasis may develop in the alveolus before extraction, indicating a need for tooth removal, or it may occur in a recent postextraction socket. In these types of clinical presentations, it will symptomatically mimic common pathological conditions such as toothache, osteomyelitis, inflammatory hyperplasia, temporomandibular joint pain, trigeminal neuralgia, periodontal conditions, pyogenic granuloma or giant cell granuloma, and thus, there may be difficulty in diagnosing such cases. A clinical sign that is usually noted in such cases, is what is often addressed to as "numb chin syndrome." This syndrome occurs because of the involvement of the inferior alveolar branch of the mandibular nerve by the metastatic niche.[2]

We report a case of a male patient who presented to our department with a proliferative, painful, swelling postextraction of the left first molar, and the lesion was present at the extraction site as well as in the mandibular anterior tooth region.

CASE REPORT

A 58-year-old male patient came to the Oral Medicine and Radiology Outpatient Department at Government Dental College, Raipur, with chief complaints of pain and swelling on the lower left side of the face and mobility of teeth in the lower jaw for more than 2 months. History revealed that the patient had got his left mandibular first molar extracted about 2 months back for treatment of a similar complaint. The patient was a habitual bidi smoker for more than 20 years.

On oral examination, the swelling was observed in relation to lower left first molar region mucosa with bone involvement and also in lower left anterior region gingivae [Figures 1 and 2]. An extraoral, irregular submental swelling was also noted due to palpable, mobile and firm

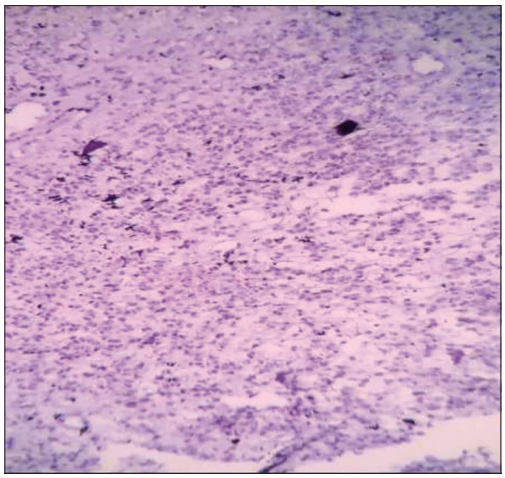

Figure 9: Cytokeratin-high molecular weight negative staining of the tissue cells

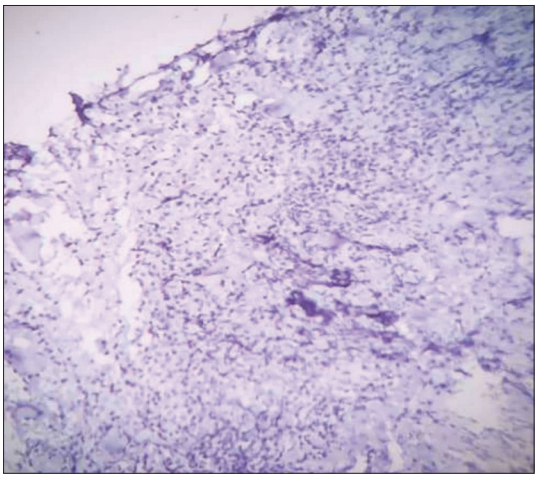

Figure 10: Cytokeratin 7 negative staining of the tissue cells

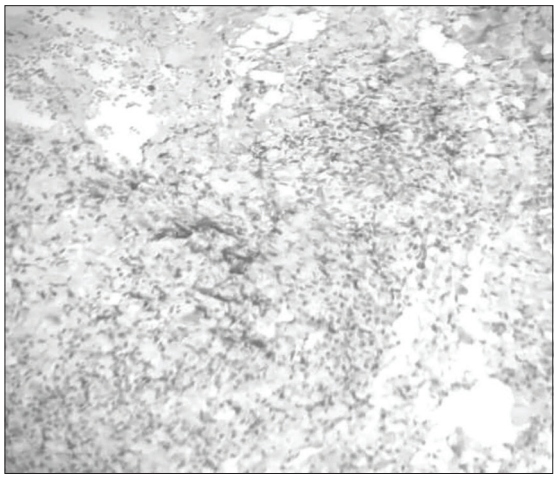

Figure 11: P63 mild positivity of tumor tissue cells

sublingual and submental lymph nodes. On inspection, a proliferative mass with surface ulceration was present in the left mandibular first molar region as well as the lower left anterior labial sulcus.

An orthopantomogram X-ray image of the patient's jaws and his lesion's clinical picture were also provided to the Oral Pathology Department. Radiograph showed an irregular, radiolucent lesion extending from the lower left central incisor to the left first molar in the mandibular alveolar region extending as poorly defined radiolucency into the body of the mandible region [Figure 3].

An incisional biopsy was sent to the Oral Pathology Department with a provisional diagnosis of osteomyelitis or carcinoma of the alveolus based on the clinical appearance of the lesion and habit history of the patient. However, since the histology did not show any feature to ascertain the provisional diagnosis, a repeat biopsy was requested with full depth of the lesional tissue.

The incisional biopsy was done again, this time with incisional tissue from both left anterior and left molar regions of the mandibular gingiva. The repeat biopsy tissue showed normal stratified squamous surface epithelium and normal, fibrocellular, juxtaepithelial connective tissue. However, deep connective tissue showed an exuberant presence of dark, large lymphocyte-like cells and vacuolar histiocyte-like cells which made the oral pathologist suspect a lymphoma or probably a leukemia.(Figures 4-8: different magnifications & microscopic fields). Blood parameter analysis of the patient for differential white blood cell count was done which was normal. This made it essential to try to find out what exactly was the lineage of these cells. Hence, immunohistochemistry (IHC) panel for lymphoma and leukemia was done which also surprisingly were negative and increased our perplexity.

Thus, histologically, this biopsy tissue was reported as an undifferentiated tumor on the basis of hematoxylin- and eosin-stained slides. This term has been used in reference to a heterogeneous group of tumors with little or no evidence of differentiation.[12]

An undifferentiated malignant tumor represents either a metastasis of unknown origin or a primary neoplasia without obvious cell line of differentiation. The terminology, "undifferentiated tumor," generally implies a high-grade malignancy, frequently associated with pleomorphic to anaplastic appearance. It is also used to describe tumors lacking evidence of lineage differentiation on the basis of routine light microscopic morphology alone.[12]

Even in undifferentiated tumors, subtle features of epithelial versus mesenchymal differentiation can often be appreciated, which assist the immunohistochemical approach to these tumors. Hints for epithelial differentiation

include epithelioid cells (round-to-oval cells) with nesting arrangement and a desmoplastic stroma with feeding vessels separating tumor cell nests. Mesenchymal differentiation is suggested by a diffuse arrangement of spindled cells, without reactive stroma, but with feeding vessels in between tumor cells. Some tumors, however, may not fit into either of these two categories because of their overlapping histologic features, for example, sarcomatoid carcinoma, melanoma, lymphoma, neuroendocrine tumors and sarcoma with epithelioid cells.[12]

IHC of undifferentiated tumors helps to categorize them into small round blue cell tumors or large cell tumors. The latter group is further divided into (a) carcinomatous tumors, (b) sarcomatous or sarcoma-like tumors and (c) tumors with overlapping features.

Each category entertains a broad list of entities from epithelial, mesenchymal, hematopoietic or melanocytic lineage in the differential diagnosis.[2]

It was only a few days later that the patient's relative mentioned that the patient was being given radiotherapy for operated prostate carcinoma that made us think in terms of metastasis. Subsequently, IHC was done to evaluate this suspicion. IHC markers used were cytokeratin 7 (CK7), CK-high molecular weight (HMW) and P-63.

CK7 and CK-HMW were negative, and P63 had a very mild and patchy positivity [Figure 9-11]. Therefore, it became clear that the gingival and alveolar lesions were metastatic lesions of prostate carcinoma.

More recently, antibodies to p63 have been reported to be more sensitive than HMW-CK for the detection of prostatic basal cells. p63, a homolog of tumor suppressor gene p53, is essential for prostate development and is selectively expressed in the nuclei of basal cells of normal prostate glands.

DISCUSSION

Metastasis is the development of secondary cancerous implants, discontinuous with the primary tumor and possibly in remote tissue. In the orofacial region, metastatic tumors are not very common, and only 1%–3% of head-and-neck cancers are those originating from distant sites.[4] In our case also, the lesion was intrabony and had then invaded the soft tissues of the gingiva and alveolus.

The mandible is more susceptible to metastatic deposits, with incidences varying from 69% to 82% lesions of all jaw metastases occurring in the mandible. Very often, metastases to the oral region is the first sign of metastatic spread (25%), and of significance is also the fact that, it can be the first indication of an undiscovered distant primary tumor (23% - 62%). The mandibular molar region is prone to metastasis, followed by the premolar area and ramus–angle region.[4] Among the bone metastases affecting the oral cavity, adenocarcinoma is the most frequent histological type.[2]

The cellular basis of site-specific tumor metastasis which by itself is an intricate biological cascade of events was first described by Paget in 1889 with his "seed and soil" hypothesis and later by Zetter in 1990. The "mechanical theory" of metastasis, which explained the spread of tumors as occurring entirely via blood flow that carries the tumor cells away from the primary site, was later given by Ewing. Hence, according to him, the secondary sites were just passive receptacles to the tumor emboli. Tumor metastasis actually is a combination of both the theories and hence is explained by the fact that neoplastic cells travel through the vascular or lymphatic system, implant into the new tissue and thrive while fighting the body's natural defense systems.[4]

According to Hart, site-specific metastasis is the process that occurs due to growth factors released from certain tissues and could therefore aid the growth of certain tumor cells while causing an inhibitory effect on others. The modes of spread of tumor emboli can be many, and they may traverse through the lymphatics, blood vessel permeation, transcoelomic permeation, local infiltration or a combination of any or all of them. In the head-and-neck region, the Batson venous plexus, which is a valve-less vertebral venous plexus, helps to bypass the filtration of the lungs and has thus become an established route of metastasis from the gastrointestinal, genitourinary and respiratory systems to the oral cavity.[4]

The oral region is usually involved by the secondary spread from other metastatic lesions, particularly from the lungs, and is not a preferred site for primary metastatic colonization. Hirshberg *et al.* stated that an important role in attracting metastatic cells to the gingiva is played by the extent and duration of the presence of inflammation in the local milieu of gingival tissues. According to the literature reviewed by some authors, the jawbones, particularly the mandible, had a greater tendency to be affected than the oral soft tissues at a ratio of 2:1.[1,5] In the present case, we could not confirm whether the lesion had spread from a secondary metastatic site or from a primary a lesion..

Furthermore, involvement of oral soft tissues is rare and mostly located in the gingiva and tongue. Breast cancer

is the most frequent metastatic oral cancer in females, and lung cancer followed by prostate cancer is the most frequent metastatic tumor in males.[2] Our patient also had a history of prostate malignancy, for which he was under radiation treatment. The change in volume of the bone with a metastatic lesion, in some cases, often correlates with the extent of dental mobility and/or with the extent of trismus present. Very often, the metastasis occurs in the extraction site, with a latency period of 2 months between the extraction and the development of the metastasis. Thus, tooth extraction can serve as a promoting factor in the metastatic process.[6,7] In the case presented here also, the lesion had evolved subsequent to the extraction of the left mandibular first molar before 2 months.

Metastatic lesions of the oral cavity are a rapidly advancing disease and have associated signs and symptoms of pain, difficulty in chewing, dysphagia, disfigurement and intermittent bleeding, all contributing to a poor quality of life, as a consequence. Hirshberg *et al*., in their literature review, noted that, in a good majority of cases, tooth extraction preceded the discovery of the metastasis.[7,8] In the case presented here also, the patient was approached for dental consultation due to continuous pain and an intraoral growth with intermittent bleeding at the site of extraction socket.

In the study by Clausen and Poulsen, they found that prostatic carcinoma is the primary source of more than 6% metastatic lesions of the mandible. Vrebos *et al*. revealed that 5% of the malignant lesions metastatic to jaws were from the prostate. Daley and Darling, in their study, evaluated 38 cases of metastatic disease, and they found that prostate carcinoma was the most common primary site (21%) for oral metastases in their study group. Van der Waal *et al*. reported similar rates of 12% prostatic cancers in 24 cases.[9,10]

Clinical manifestations included pain, bony- or soft-tissue swelling and loose teeth, but some lesions tend to be asymptomatic. The most common clinical findings as quoted by most researchers were paresthesia of the lower lip, a mass growing from a nonhealing extraction site and multifocal lesions. Metastatic disease is considered by most researchers to be a disease of the middle aged and elderly. It is noteworthy therefore that all studies consistently showed a significantly greater frequency of oral metastasis in patients over 50 years of age.[2,10]

The histopathology of these lesions is very important in detecting the connection between primary tumor and metastasis. Histopathologically, in cases of poorly differentiated adenocarcinoma or carcinoma, bone metastases of unknown primary tumors are difficult to ascertain and so monoclonal antibodies specific to CK subtypes are often used to classify tumors according to their parent tissue of origin.[11,12]

CK7 is, therefore, useful to identify the organ origin of adenocarcinomas. Besides, it also differentiates benign prostate tumor stained positive versus prostate cancer stained negative. It is normally expressed by most ductal, glandular and transitional epithelium.

Cytokeratins

CKs are an intermediate filament (If) group of cytoskeletal proteins that are a major component of the epithelial cytoskeleton. They are grouped into two categories, based on the amino acid sequence and charge of the keratin proteins.

- Type I (acidic, CK10, CK12–19, 40–56.5 kDa)
- Type II (neutral-basic, CK1–CK8, 53–67 kDa).[13]

Genes for Type I CKs are expressed at 17q21.2, Type II genes at 12q13.13. A pair of keratin proteins, consisting of one keratin protein from each group, are always coexpressed and build heteropolymers to form the 10-nm keratin intermediate filaments (I.Fs) that are part of the cytoskeleton.[14]

The two most common CK stains are CK7 and CK20; the combination of their immune profiling proves helpful to identify primary tumor sites. The CK7/CK20 phenotype is, especially useful in clinical situations, exemplified by the requirement to differentiate between prostate and urothelial (CK7/CK20 variable) carcinomas because CK profiles of prostate adenocarcinoma are usually negative for both CK7 and CK20.[12]

CK-HMW is especially useful in the interpretation of difficult prostate biopsies. It is a well-known fact that the identification of an associated CK-HMW-positive basal layer in an atypical small gland proliferation excludes the possibility of invasive prostate adenocarcinoma.[15] On the other hand, invasive prostate adenocarcinomas do not contain an associated CK-HMW-positive basal layer around the proliferating neoplastic small glands of interest. Thus, CK-HMW cytokeratin can be useful in differentiation of metastatic squamous cell carcinomas and adenocarcinomas. The stain recognizes and reacts to CK1, CK5, CK10 and CK14 when present.

In our case, P63 showed a very mild positivity, so, as reported by previous researchers, we believe that this was due to a contrast to usual-type prostatic adenocarcinomas,

in which there is no p63 expression. These tumors are unusual because they express this benign basal cell marker in a nonbasal cell distribution. The HMW CKs (34BE12 and CK5/6) along with p63 are effective markers for basal cells. It is difficult to prove a complete absence of basal cells, but, if the sample is large enough, it can be confirmatory of carcinomas. It is noteworthy that a subset of atrophic carcinomas express p63 in the malignant cells but, in them, HMW keratin staining is negative, as was seen in our case.[13]

In the majority of patients, as in our case, that present an oral metastasis, the primary tumor has generally been well diagnosed and treated. Sometimes, the diagnosis of primary lesions may be difficult.[2] Also important is the fact that, metastatic lesions are related to the advanced stage of a malignant disease and to malignancies with a high degree of histological aggressiveness. The cells of such tumors experience five steps of: growth at primary site, intravasation, endothelial or sub-endothelial basement membrane adherence at a secondary site followed by parenchymal invasion & proliferation at the secondary site for a successful metastatic colony formation. The five steps are governed by endothelial adhesive determinants, chemotactic factors and growth factors that are specific to an organ leading to site-specific metastasis. This fact explains the difficulty of diagnosis & curative treatment, and hence, these injuries are usually classified as reserved and ones with dark prognosis.[14,16]

Therefore, it gets re-emphasized that a thorough and proper history taking along with an awareness of likely metastatic lesions is extremely essential and gives direction with less time consumption to the relevant diagnosis of the case. A thorough clinical, biochemical, hematological examination together with radiographs and histopathology should be carried out in an elaborate manner for each patient, as patients may have similar clinical manifestations, in spite of a differing set of pathological background and vice versa. In cases with symptoms of unexplained facial pain and numbness also, an awareness of a possible metastatic lesion is crucial and so requires to be included in the differential diagnosis to rule out.[2,9]

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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Nil.

Conflicts of interest

There are no conflicts of interest.

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