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REVIEW ARTICLE

Metastatic Tumors of the Oral Cavity

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ABSTRACT

The pivotal reason for morbidity and mortality of any type of cancer is due to metastasis that occurs as a result of adaptation of genetically unstable cancer cells, in an ectopic conducive environment. Oral metastasis in spite of being unusual or rare represents around 25% of the first signs of metastatic spread. Literature says there are more number of cases of jaw bone metastasis reported than in the oral soft tissues. The most common primary organs metastasizing to the jaw bones and the oral soft tissues are the breast and the lungs respectively. The issue in diagnosing a metastatic tumor arises either when the patient does not reveal the history of the primary illness he or she may be suffering from or when he or she is unaware of it. Diagnosis in such situations is a challenge to the clinician or pathologist. Diagnosing any lymph node or distant metastasis from oral cancer is very important for the prognosis of the patient. In this review we have made an attempt, to explain some recent concepts of pathophysiology of the metastatic process, the clinical manifestations of metastatic tumors to the oral region and to discuss their diagnostic workup.

Keywords: Metastasis, Oral region, Oral cancer, Angiogenesis, Cancer stem cells

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INTRODUCTION

Invasion and metastasis are the most important causes of cancer related morbidity and mortality and are the biological hallmarks of malignant tumors.[1] Although millions of cells are released by the tumor into the circulation, healthy tissues have a sound defence mechanism that put up a good fight against these tumor cells. However a tiny population of these cells may sometimes metastasize to distant organs. Metastasis is a co-ordinated process consisting of several discrete steps.[1,2] Metastasis to the oral cavity is a rarity, making up only 1% of all oral malignancies and is associated with poor prognosis. There have been more cases of metastasis to the jawbones than to oral soft tissues, recorded in literature.[3,4] These metastatic tumors more often than not turn out to be carcinomas than sarcomas.[5] The most common primary sources of metastatic tumors to the oral region are the breast, lung, kidney, bone, prostate and colon. Diagnosing a metastatic tumor of the jaw is a real challenge and its diagnosis being of utmost importance due to the fact that it may be the first indication of an undiscovered malignancy at a distant site.[6] Likewise, oral squamous cell carcinoma (OSCC), one of the most common epithelial malignancy in the head and neck region, has a significantly high recurrence rate, frequently metastasizes (40% of patients) to the cervical lymph nodes.[7]

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UNVELING THE PATHOPHYSIOLOGY OF METASTATIC DISSEMINATION

There are several discrete, complex and interrelated steps in the process of cancer metastasis, wherein, the tumor fails to metastasize if any step in this cascade misfires. The major steps are as follows[2,8,9] (Fig. 1).

Though clinical observations say that carcinomas spread through lymphatics and sarcomas through hematogenous route, this concept is not valid anymore due to the presence of numeros venolymphatic anastomoses (Fig. 2).[10]

TUMOR HETEROGENEITY

Cancers, in order to survive and metastasize, have to evolve and become heterogeneous. Nowell had proposed that the acquired and accumulating mutations within the tumor, together with selection pressures would result in the adaptation of the tumor cells, making them heterogeneous and plastic, in order to develop strategies to survive a hostile environment and use these resources to grow and proliferate.[8] Evidence now says, this contribution toward the plasticity of the tumor cells could also be via epigenetic mechanisms.[11] There are two general models of heterogeneity of cancer cells. They are: (1) Clonal evolution model that Nowell had proposed. (2) Cancer stem cell model that states that cancer cells have only limited proliferative potential. It is a small subset of population called cancer stem cells (CSC)

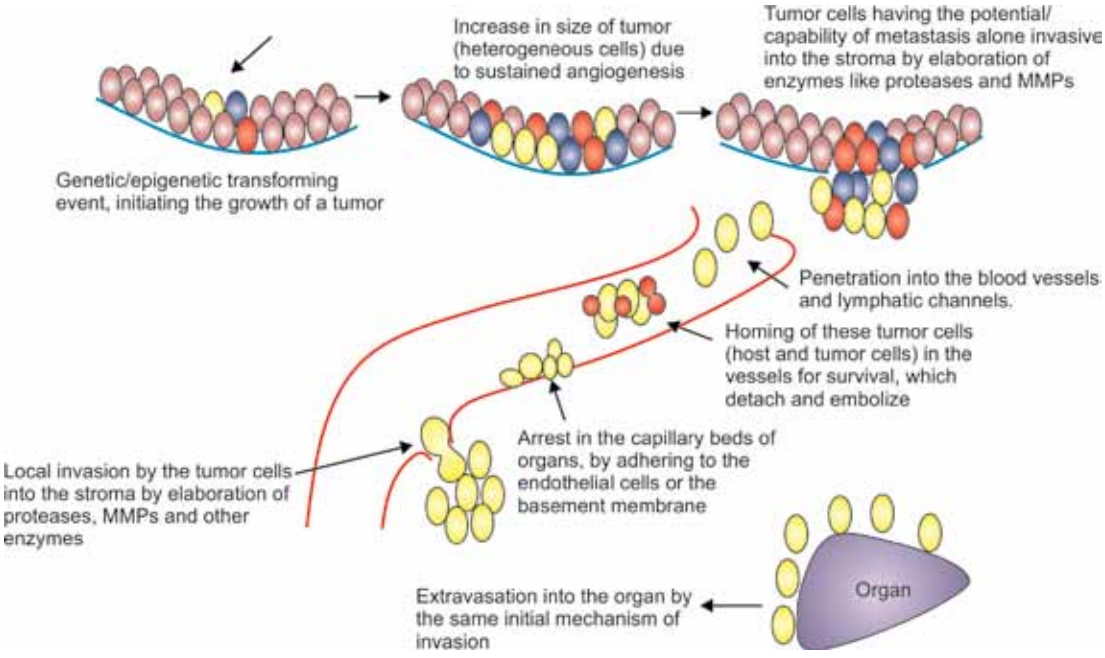

Fig. 1: Metastatic cascade

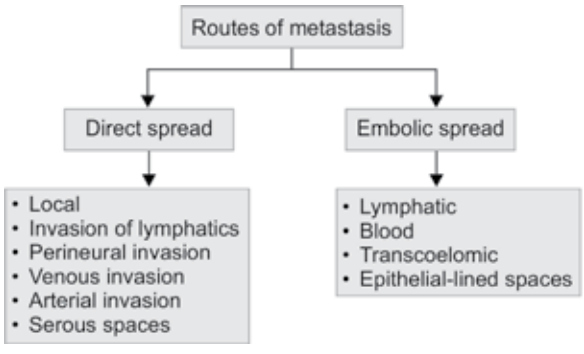

Fig. 2: Routes of metastasis

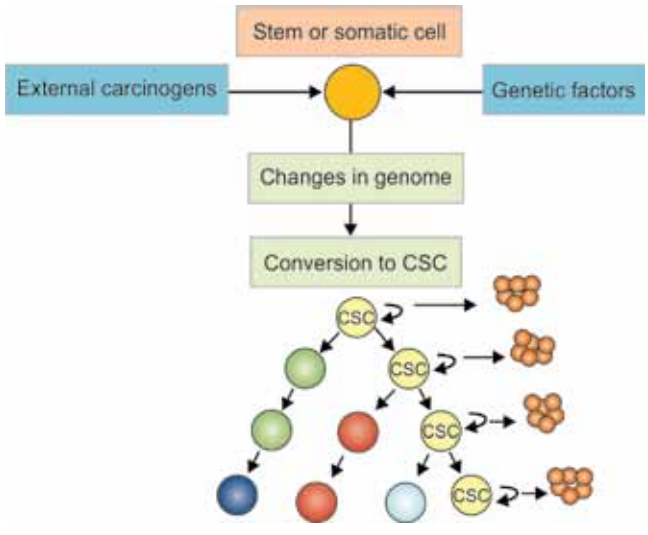

Fig. 3: Cancer stem cell model: CSCs self renew and proliferate

that consistently proliferate and give rise to new tumors. Proponents of this hypothesis say that certain properties of stem cells make them quintessential to accumulate the genetic or epigenetic changes needed for tumorogenesis. It is this small population that have the different properties of cancers like drug resistance, invasion and metastasis[12-14] (Fig. 3).

ANGIOGENESIS

Once the tumor cells, irrespective of their origin, have become defiant to the host's immune/regulatory mechanisms, the growth and metastatic spread of the cancer cells depends on a rich vascular supply. Cancer cells can stimulate neo-angiogenesis, during which new vessels sprout from previously existing capillaries, or, in some cases can stimulatevasculogenesis, in which endothelial cells arise from the bone marrow. Tumor angiogenesis is basically a four-step process.

1. The basement membrane in tissues is injured locally. There is immediate destruction and hypoxia.
2. Endothelial cells activated by angiogenic factors migrate.
3. Endothelial cells proliferate and stabilize.
4. Angiogenic factors continue to influence the angiogenic process.

Data derived from examinations of human lung cancer, brain metastases indicate that tumor cell division takes place within 75 μm of the nearest blood vessel, whereas tumor cells residing beyond 150 μm from a vessel undergo programmed cell death.[8] This process is stimulated as and when tumor cells need nutrients and oxygen. This is achieved by inducing an imbalance between the angiogenic stimulators and inhibitors, i.e an increase in the angiogenic inducers and a decrease in the inhibitors. Several inducers and inhibitors have been identified. Some important angiogenic inducers are—vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), angiogenin, transforming growth

factor (TGF)-α, TGF-β, tumor necrosis factor (TNF)-α, platelet-derived endothelial growth factor, granulocyte colony-stimulating factor, placental growth factor and interleukin.[8] There are many naturally occurring proteins that can inhibit angiogenesis—angiostatin, endostatin, interferon, platelet factor 4, thorombospondin, prolactin 16 kd fragment, and tissue inhibitor of metalloproteinase 1, 2 and 3.[8,15,16]

APOPTOSIS INHIBITION

Metastasis is a highly inefficient process, where very few cells successfully metastasize. The induction of apoptosis is a prophylactic measure to avoid metastasis. There is sufficient evidence in literature to apprise us about the anti-apoptotic measures of tumor cells. This is significant due to the fact that circulating cancer cells have to pass through several stressful steps, including survival in the bloodstream, arrest in the capillary bed and resumption of proliferation in distant organs.[17]

NOTE ON THE ROLE OF miRNAS

MicroRNAs (miRNAs) are a group of endogenous, non-coding, 18 to 24 nucleotide length single-strand RNA molecules. miRNAs play crucial roles in regulating fundamental cellular biological processes such as cell cycle, differentiation and apoptosis. Many recent molecular studies of head and neck cancer and OSCC specifically have revealed the deregulation of miRNAs. The recent explosion of new literature pertaining to miRNAs have shown that miRNA expression profiles could explain the pathogenesis, metastasis and chemoresistance of cancers. miRNAs involved in metastasis could be prognostic markers and therapeutic targets in metastatic tumours. Liu et al, using microarray analysis, identified that reduced levels of miR 138 and 222 enhanced the metastatic potential of tongue squamous cell carcinoma. Chang et al observed that increased expression of miR 211 was associated with advanced nodal metastasis and vascular invasion of oral squamous cell carcinoma. Lajer et al and Liu et al, have demonstrated the inhibiton of, factor inhibiting-hypoxia inducible factor (FIH) by increased expression of miRNA 31 thereby indirectly promoting metastasis. Besides, miRNAs are also implicated in maintaining the stemness of stem cells which may become oncogenic if, over or under expressed. Various other miRNAs implicated in metastasis aremiRNAs 27a, 29a, 30d, 143, 145,328.[18-20]

METASTASIS TO THE ORAL CAVITY

Metastatic lesions to the oral region are rare as they are not a favoured target. They are more often a secondary spread from other metastatic lesions. It was proposed by Batson that the valveless vertebral plexus could be the rationale behind metastasis to the head and neck region. Studies state that the metastatic process could be a site-specific event more than being a random event. What, then, could be the driving force behind primaries of various organs metastasizing to the oral cavity? Jaw bones with active marrow attract cancer cells. Metastasis to the jaw bones usually manifests in older adults. However, remnants of hematopoietic active marrow detected in the posterior region of the mandible may be the reason. Also, chronic inflammation and the rich network of capillaries in the gingiva may play an important role in attracting tumor cells. The proliferating capillaries with their fragmented basement membranes, make them vulnerable to the penetration of metastasizing cancer cells.[3,21,22]

EPIDEMIOLOGY

Metastatic tumors to the oral cavity are very rare representing only 1% of all neoplasms in the oral region. In 25% of the cases oral metastasis is found to be the first sign of metastatic spread. Table 1 summarizes the epidemiology of oral cavity metastasis.[3,17,21,22]

NOTE ON METASTASIS FROM ORAL CAVITY

Oral squamous cell carcinoma (OSCC), being one of the most common tumor of the head and neck (38%), has a significant recurrence rate with frequent metastasis to the lymph nodes (occurring in about 40% of the patients). Lymph node metastasis is very characteristic of OSCC and is considered as the first sign of spread. Level I to level III nodes are the most common sites for neck node metastasis for OSCC (anterior to circumvallate papillae), whereas level II to IV are involved in cancers of the oropharynx, hypopharynx and larynx. The incidence of distant metastases in head and neck squamous cell carcinoma (SCC) is relatively small in comparison to other malignancies (Table 2). The reported frequency of distant metastases in patients with HNSCCs, ranges between 6 to 43% in autopsy cases and 8 to 17% in clinical studies according to Betka's review. Distant metastasis accounts for only 10% of the cases, manifesting commonly in lung, bone, liver and skin. However, the overall incidence of distant metastases is 20% according to Hsu LP et al. Literature with regards to distant metastasis from the oral region is minimal with information conveyed through different case reports. Studies have been done in order to assess the risk factors for distant metastasis. Locations of distant metastases differ among the various primary tumor sites. The lungs are the most-common site of distant metastasis for patients with hypopharyngeal cancer and oropharyngeal cancer. For OSCCs metastasis to bones and lungs is reported to beequal. Preoperative clinically palpable neck

Table 1: Epidemiology of oral metastatic tumors

Age	
Mean age of patients with metastatic tumors	40 to 70 years
Age group with oral soft tissue metastasis	Older age group (mean – 54 years)
Age group with oral jaw bone metastasis	Younger age group (mean – 45 years)
Common primaries and their predilection	
Most common sources of metastatic tumors	Lung, breast, kidney and bone.
Most common primary site	Lungs – oral soft tissue Breast – jaw bones
Jaw bones vs oral soft tissues	
Jaw bone: Oral soft tissue predilection	2:1
Jaw bone predilection	Mandible > maxilla
Most common oral soft tissue preferred	Dentulous patients – Attached gingiva Edentulous patients – Equal for tongue and alveolar mucosa
Sex	
Male: Female predilection	Equal for jaw bones 2:1 for oral soft tissues

Origin of metastasis to the oral mucosa / jaw bone	*Male*		*Female*	
	Oral mucosa	*Jaw bones*	*Oral mucosa*	*Jaw bones*
Lung	31%	25%	9.4%	
Breast	—	—	24%	36.6%
Kidney	14%	10%	12%	8.5%
Prostate	—	7.5%	—	—
Skin	12%	—	6.8%	—
Liver	7.5%	8.6%	—	—
Colorectum	4.2%	4.7%	6.8%	7.1%
Bone	5.2%	7.5%	9.4%	6.7%
Testis	4.5%	4.4%		—
Esophagus	4.5%	3.6%		—
Stomach	3.7%	2.5%		—
Genital organs (uterus, ovaries, cervix, fallopian tubes)			14	9.5%
Thyroid			5.4%	

Table 2: Metastatic incidences from the oral cavity to distant organs

Authors, Year, (Number of Cases, HNSCC) and Results (% of Distant Metastasis)				
Probert et al,[28] 1974, (n = 96;31% OSCC)	*Merino et al, 1977,[29] (n = 546;21% OSCC)*	*Papac et al,[30] 1984, n = 52*	*Leon et al,[31] 2000, (n = 64;2% OSCC)*	*Kowalski et al,[32] 2005, n = 89*
Lung-65%	Lung-52%	Lung-75%	Lung/Mediastinum-52%	Lung-58.4%
Bone-25%	Bone-20.3%	Bone-44%	Bone-12%	Bone-37.1%
Liver-24%	Liver-6%	Liver-17%	Liver-5%	Liver-3.4%
Skin-14%	Mediastinum-2.9%	Skin-13%	Combination of lung with bone and liver or skin-31%	Brain-3.4%
Brain-13%	Others-15.4%	Brain-13%		Peritonium-1.1%
Adrenal-8%		Adrenal-6%		Mediastinum-1.1%
Heart-7%		Heart-8%		Axillary lymph nodes-1.1%
Kidney-6%		Kidney-10%		

disease (N1-N3) with histological evidence of metastasis, extra-capsular spread, the presence of the lympho-vascular invasion and three or more positive lymph nodes are an added risk for the development of distant metastases.[23-27]

COMMON COMPLAINTS AND CLINICAL PRESENTATION

Oral metastasis is usually a late complication, with its clinical presentation differing with different oral sites. Its diagnosis may be variable and may cause difficulties and also errors in diagnosis. Some of the common complaints that the patient comes to the dentist with are: pain, bleeding,dysphagia, interference with mastication, disfigurement, swelling, loss of sensation (paraesthesia), bleeding.[17,21,33-38]

A very rare manifestation, metastasis to the oral cavity represents only 1% of all neoplasms in the oral region, with the jaw bones being affected more frequently than the soft tissues. Metastatic lesions in the oral region can cause considerable discomfort to the patient affecting their daily routine.

LESIONS IN THE ORAL SOFT TISSUE

Gingiva is the preferred oral soft tissue for metastatic tumors because of its blood supply and chronically inflamed nature. Edentulous patients have an equal distribution between the tongue and the oral mucosa. It usually occurs as a hyperplastic or a reactive growth on the gingiva. The lesions can vary from being exophytic, ulcerative or haemorrhagic growths. Submucosal masses on the tongue have also been reported. An unusual, untypical manifestation is an exuberant soft tissue growth in the extraction socket. It is thought that extraction may have stimulated the metastatic process to the site or it might have been present in the area before extraction, causing tooth mobility. It is important for the clinician to differentiate, metastatic lesions from other lesions like pyogenic granuloma, peripheral giant cell granuloma, fibro sarcoma (cheek), leiomyoma (tongue).[17,21,33-39]

LESIONS IN THE JAW BONE

In jaw bones the common location for metastasis is the mandibular molar area, followed by the premolar area. Swelling with tenderness and pain, paraesthesia, pathological fractures, tooth mobility and trismus are common symptoms. Patients having paraesthesia (mandible) or numb chin syndrome, in the absence of any other possible disease process, should be given special attention, as it signifies invasion into the bone and involvement of the inferior alveolar nerve. Central giant cell granuloma, carcinoma alveolus, intraosseous squamous cell carcinoma, estrogenic sarcoma are some lesions to be considered in the differential diagnosis.[3,17,21,33-40]

DIAGNOSTIC WORKUP

It is very important for the dentist to follow a structured approach in order to diagnose metastatic tumors in the oral region, so that no relevant data or information goes unnoticed.[41]

Review Clinical History

What can history reveal? Does it help raise suspicion of a metastatic lesion?

- Most data, present in the form of isolated case reports, say that patients with metastatic tumors in the oral region chiefly complain of a growth on the gingiva which may or may not be associated with pain and bleeding.
- Swelling of the jaws, especially the mandible, is a common complaint which most often is associated with pain.
- Usually, these lesions may cause a lot of discomfort and lead to a poor quality of life.
- Mobility of teeth and loss of sensation (paraesthesia) are two complaints which raises the suspicion of a metastatic lesion.
- An additional clue is the age of the patient, who is often between 40 to 70 years of age.
- The duration of the lesion on an average, ranges from 2 weeks to 2 months.
- Past medical history of a malignancy.[3,17,21,33-40]

Clinical Examination

History does not always give us an impression of metastasis. How far can clinical examination and scrutinization be useful?

- Most metastatic lesions (gingival growths) on palpation are painful and hemorrhagic (not always though).
- These growths often resemble hyperplastic or reactive lesions like pyogenic granuloma.
- Soft tissue lesions manifesting on the tongue do so, often, as a submucosal mass.
- Check for bony swelling. Bony expansions are accompanied by tenderness over the affected area or a constant dull pain and paraesthesia.
- Check for lymph node enlargements—mobile or fixed.
- At times one encounters a soft tissue mass extruding from a recent extraction wound. This is a strong clue for the clinician.[3,17,21,33-40,42]

Once clinical examination is done and past history of a tumor is elicited, obtain the respective slides and reports for review.

Specific History

More often than not, it is during clinical examination that one suspects a metastatic lesion, unless and otherwise the patient himself or herself gives a specific history of a previous tumour elsewhere. What is the next step after the clinician suspects a metastatic process?

- The clinician should try and ask for specific questions with regards to the primary he or she may be suspected to be suffering from.
- Cough with hemoptysis and dyspnoea may indicate lung cancer.
- Pancoast tumor represents fewer than 5% of all primary lungcancers.
- 95% of Pancoast tumors are non-small cellcarcinomas, most commonly squamous cell carcinomas (52%), or adenocarcinomas (23%), and large cell carcinomas (approximately 23%). They can cause shoulder and upper extremity pain and weakness or atrophy of the ipsilateral hand and Horner's syndrome (ptosis, miosis, enophthalmos, and anhidrosis).

- Hematuria, weight loss, abdominal pain may signify a renal cell carcinoma.
- Increased frequency, difficulty of urination associated with high fever, points towards prostate cancer.
- Rectal bleeding, constipation indicative of colo-rectal carcinoma.[43-48]

Note: The clinician should be careful not to over-diagnose any condition.

Evaluate available Radiographic Material

Do radiographs help? Are they pathognomonic for any metastatic lesion?

- Metastatic tumors unfortunately, have no pathognomonic radiologic feature.
- Cardinal radiographic signs of metastasis are either an osteolytic or an osteoblastic lesion.
- *Osteoblastic lesions:* Typically seen in prostate cancers.
- *Osteolytic lesions:* Seen in other primaries like breast, lung, kidney and thyroid.
- Radiolucencies may be well to poorly circumscribed, the latter also known asmoth-eaten appearance.
- There are many case reports stating other ancillary findings like, periapical lesions mimicking cysts, loss of lamina dura and pathological fractures.[49-52]

Obtain Biopsy and Evaluate Light Microscopic Features

What do biopsies tell us? Are they confirmatory?

- Diagnosis is invariably based on histologic findings.
- A metastatic tumor resembles its primary.
- If previous slides of the primary are available, a comparison with the current histologic findings can be made.
- In some cases, the histologic appearance is poorly differentiated making the diagnosis very difficult. In such cases screening using a panel of immunohistochemistry stains can smoothen or ease the diagnosis. Few examples:

  Breast carcinomas: Positive for CK7
  Negative for CK 20, thyroid transcription factor (TTF 1) and prostate specific antigen (PSA).

  Lung carcinoma: Postive for CK 7 and TTF 1

  Colorectal carcinoma: Positive for CK 20
  Negative for CK 7, TTF 1 and PSA

  Prostate carcinoma: Positive for PSA

- One has to pay close attention while evaluating histopathological findings, as some intra-oral primaries resemble tumors in various other organs.

  Some conundrums:

  – Primary ductal carcinoma of salivary gland versus metastatic breast carcinoma.
  – Primary intraoral clear cell carcinoma versus metastatic renal cell carcinoma.
  – Primary intraoral squamous cell carcinoma versus metastatic squamous cell carcinoma from the lung.
  – Primary intraoral malignant melanoma versus metastatic malignant melanoma.[3,53-58]

Laboratory, Specific and Special Investigations

Is histopathology and IHC enough? Don't we have to investigate further, just to make sure?

- A plethora of specialized techniques are available for further investigations.
- Laboratory tests include complete blood count, liver function tests like albumin, bilirubin total protein, alkaline phosphatase, ALT (Alanine Amino Transferase) and AST (Aspartate amino Transferase), calcium level, urine analysis, renal function tests like creatinine, urea, total protein, albumin, uric acid, phosphate, calcium, bicarbonates, potassium and sodium levels and thyroid function tests like T3, T4 and TSH.
- Specific investigations can be performed, based on the primary tumor suspected.
  – A chest radiograph or CT for lung.
  – Serum Prostate Specific Antigen (PSA) assay for prostate.
  – Papanicolaou (PAP)smear for cervix.
  – Mamography for the breast.
  – Ultrasound/ CT of abdomen for liver, pancreas, adrenal, kidney, gallbladder, ovary, stomach.
- Special investigations like Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT) and bone scintigraphy can be done to check for distant metastasis.[39]
- *PET:* Is a nuclear medicine, functional imaging technique that produces a three-dimensional image of functional processes in the body. Fluorodeoxyglucose or FDG a form of radioactive sugar is injected into the blood. Cancer or tumor cells absorb high amount of sugar because of their metabolic activity. After about an hour, a special camera makes pictures of areas of radioactivity in the whole body, thus helping in detecting metastatic spread anywhere in the body.
- *SPECT*: Is a nuclear medicine tomographic imaging technique where gamma rays are used. ECT is similar to PET in its use of radioactive tracer material and detection of gamma rays. In contrast with PET, however, the tracer used in SPECT emits gamma radiation that is measured directly. SPECT scans, however, are significantly less expensive than PET scans, in part as long lasting, more easily-obtained radioisotopes than PET can be used.

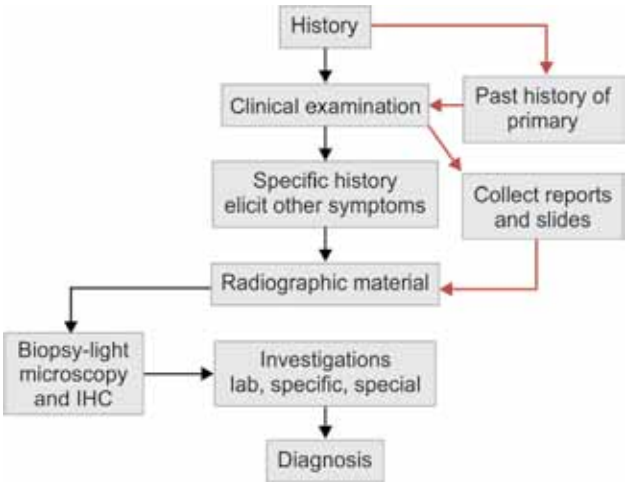

Fig. 4: Schematic representation of diagnostic workup

- *Bone scintigraphy*: A bone scan or bone scintigraphy is a nuclear scanning test to find certain abnormalities in bone. It is primarily used to help diagnose a number of conditions relating to bones, including: cancer of the bone or cancers that have spread (metastasized) to the bone.[59-61] Figure 4 shows a step-wise method to go about diagnosing a metastatic tumor in the oral region.

DEFINITIONS USED TO DESCRIBE STAGE AND SIZE OF DEPOSITS

Some important terminologies that a clinician/pathologist should be acquainted with:[62]

Isolated Tumor Cells (ITCs)

In any single node, collections of tumor cells totalling not more than 0.2 mm in greatest dimension in the nodal parenchyma, sinuses or capsular/perinodal vessels (microemboli).

Micrometastasis

In any single node, single or multiple tumor deposit(s) confined within the node capsule, totalling between 0.2 and 2.0 mm in greatest dimension; may show evidence of growth (mitotic activity), but desmoplasia is often absent.

Conventional Metastasis

In any single node, total profile diameter of tumor deposit(s) exceeds 2.0 mm; may be accompanied by desmoplasia.

Occult (Covert) Metastasis

Any metastatic deposit not suspected clinically, may be ITC, micrometastasisor conventional metastasis.

Skipping

Metastases at noncontiguous nodal levels.

Peppering

ITCs/micrometastases in multiple levels; conventional metastasis is absent.

Fast-tracking

Metastasis via multiple drainage routes, often directly to remotelypositioned nodal groups.

TREATMENT AND PROGNOSIS

A metastatic process always represents a poor overall prognosis. Palliative treatment is the need of the hour, in order to reduce patient's pain and preserve oral function. However if the primary has been treated and the patient is not completely cured, the oral metastatic lesion could be treated aggressively. Treatment can be done by radiotherapy, chemotherapy or by surgical excision.

CONCLUSION

Detection of an oral metastatic process is a challenge to the oral pathologist. The pathologist should be diligent and receptive when such cases are encountered. Diagnosing an oral metastatic lesion becomes straightforward if the patient gives a history of a primary. The test is when the patient does not give adequate history or is unaware of one. Diagnosis of an oral metastatic lesion in such cases becomes important as it can help in detection of an occult primary malignancy elsewhere in the body.

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