ARTEFACTS

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ABSTRACT

Biopsy is defined by Shafer and others, as "the removal of tissue from the living organism for the purpose of microscopic examination and diagnosis." The proper obtaining & handling of soft tissue specimens is essential & obvious for accurate histopathologic diagnosis. Both quality as well as quantity of the specimen as well as the competence of histo-technician equally aid the ability of oral pathologist in interpreting accurate diagnosis. It is not always possible to produce a stained microscopic slide of the tissue that exactly represents their accurate structure in life. The artefacts can compromise the exact interpretation of tissue specimen. The artefact is any structure or feature that is not normally present in the living tissue & which occur at any stage beginning from the time of biopsy to the final stage such as surgery, fixation, processing, embedding, microtomy, staining procedure, mounting.

It is therefore necessary to identify the common artefacts during interpretation of oral soft tissue biopsies. The present article attempts to enlighten the reader of the various types of artefacts encountered at various stages, to provide a guide for their recognition, their possible causes and also possible ways to minimise the same.

Key Words: Artefacts, Biopsy, Histopathology, Difficulty in diagnosis.

INTRODUCTION

Biopsy is defined by Shafer and others, as "the removal of tissue from the living organism for the purpose of microscopic examination and diagnosis." In general, biopsies are simple office procedures that can be rendered by any dentist who is aware of its rules and precautions.[1] A biopsy consists of the obtaining, proper handling of soft tissue from living organism for the purpose of examining it under microscope & which ensure the pathologist receives a representative sample of the lesion, in order to establish an accurate diagnosis.[2]

Numerous types of artefacts can affect biopsy specimen at any stage beginning from the time of biopsy to the final stage of mounting.[4]The sequential steps of biopsy rendered in the management of oral lesions include, adequate data collection, competent diagnostic skills, proper surgical management, evaluation and interpretation of the pathologist's report and comprehensive patient follow up.[2]

In histological & cytological terms artefact is defined as being any structure or feature that is not normally present in the living tissue. These are unrelated, self-colored artificial feature found in tissue sections.[4,5]

The problem is recognizing artefacts as such when they do occur & not confusing them with normal tissue components or pathological changes. In some situation presence of an artefact can compromise an accurate diagnosis.[4] These artifacts can be minor which do not interfere with the pathologists' ability to provide an accurate diagnosis. In some cases however, the degree of artifactural damage is excessive or may involve the entire specimen, rendering it substandard or useless for diagnostic purposes.[5,6]

The aim of the present article is to promote awareness of the various artefacts which may be encountered in histopathology, to provide guide for their recognition, & to suggest, where possible, the means by which their occurrence can be avoided.

Tissue alteration is a major problem experienced by the oral pathologist which may hind proper biopsy & subsequent definitive histopathologic interpretation.[7]

Artefacts broadly categorized as follows;

1. **Prefixation artefacts**
   I. Before biopsy/surgery –
      a. Due to surface preparation
      b. Due to topical application of medicaments
      c. Due to intralesional inj. of local anaesthetics
   II. During biopsy/surgery –
      a. Due to surgical instruments –
         Split artefacts
         Squeeze artefacts
         Crush artefacts
      b. Curling artefacts
      c. Due to presence of suture material
      d. Gelfoam artefact
      e. Due to foreign body contamination
      f. Starch artefact
      g. Fulgeration artefact
2. **During transport –** Freezing artefacts
3. **Fixation artefact –**
   a. Ice crystal artefact
   b. Due to chemical changes
   c. Shrinkage artefact –
      Due to delay fixation
      Due to prolong fixation
   d. Pigmentation artefact
   e. Streaming artefact
   f. Diffusion artefact
   g. Due to false localization of extraneous material
   h. Microwave fixation
4. **De-calcification artefacts**
5. **Tissue processing artefacts**
6. **Poor processing artefacts**
7. **Impregnation artefacts**
8. **Embedding artefacts**
9. **De-calcification artefacts**
10. **Staining artefacts**
11. **Mounting artefact**
12. **Miscellaneous artefacts**
13. **Artefacts in diagnosis**

PREFIXATION ARTEFACTS:

Preparation of biopsy area –

Sometimes coloring agents are used to mark excision margins at biopsy site & also used to mark margins of fixed surgical specimen, later is done to orient specimen appropriately & to assess

these margins under microscope. Some commonly used coloring agents are india ink, silver nitrate, alcian blue, alcian green.[2,4,5,8] Preparation of biopsy site with tincture iodine or other coloring agents should be avoided or if may used then this should be mentioned completely, since it may interfere with some procedures like tissue processing & staining.[6,7,8]

Artefacts due to topical application of various medicaments to the lesion by the patient or by the clinician alter the tissue which may lead to unnecessary deposits on the tissue.[7]

Local anaesthetic infiltration into the lesion while excision or incision should be avoided because it may cause haemorrhage leading to distortion of the tissue relationship, extravasation, separation of connective tissue band with vacuolization of epithelium.[2,6,7,8] This should be avoided by giving injection 3-4 mm away from the lesional site with 4 cardinal reference points (top, bottom, left, right) with adequate quantity of anaesthetic solution.[2,5,6,8]

Artefacts due to surgical instruments –

Split artefact –during biopsy multiple cuts may given in the tissue which result in split artefact between epithelium & connective tissue giving false interpretation of vesiculo-bullous lesion. This can be prevented by avoiding excess pressure caused by suture traction.[6]

Squeeze artefact –

Even the most minimal compression leads to tissue distortion that groups together crush, haemorrhage, splits, fragmentation. Thid results during the use of stitch for traction or by dull scalpel blade. Here pseudomicrocysts results as a result of surface epithelium forced inward through connective tissue by toothed forcep.[6,9,10,11,12] This can be avoided by careful handling of the specimen by the forceps.

Crush artefact/ Compression artefact –

These artefacts result from even the minimal compression given to the tissue, mainly when toothed forcep is used to hold it. These are more common in incisional than punch biopsy.[6,13] Crushing produces destructive type of tissue distortion, that rearranges tissue morphology & squeezes dark chromatin out out of the nuclei giving misdiagnosis of dysplastic lesions.

These can be prevented by 1. Careful handling of the specimen especially at the base. 2. Use of blunt forceps rather than toothed forceps.

Curling artefact –

These artefacts observed commonly in incisional biopsy. It creates lesser problem in case of thin section but having relatively thick keratotic surfaces.

If specimen is too small, fixation in formalin causes curling & bending due to shrinkage of specimen, thus making difficulty in its orientation during embedding procedure.

These artefacts can be prevented by, 1. Ensuring adequate depth of specimen 2.If specimen is small, placing it with its mucosal surface up on a piece of sterile paper & allow to remain unfixed while the incision is being sutured.

Artefacts due to presence of suture –

It is an occasional inclusion in histologic specimen, though may not be of any pathologic significance. But when remains in the specimen, it can damage the microtome knives leading to tear in the section. Silk sutures exhibit strong birefringence under polarised light. By removing visible sutures wherever possible these artefacts can be minimized.

Gelfoam artefacts – gelfoam or surgical sponge are sometimes used to control bleeding during surgical procedures. In histologic sections with gelfoam appear as distorted spaces filled with the blood surrounded by slightly basophilic gelatin wall of varying thickness.

Artefacts due to foreign body contamination –

These artefacts often make diagnosis of specimen quite difficult. Paper, cotton, guaze or cork board should be used during specimen preparation contribute to this & usually found on the surface of epithelium. Presence of cotton in the histologic section may resemble eosinophilic amyloid like or black substance & polarizes under polarized light.

Amyloid like material is highly characteristic of odontogenictumors, thus resulting wrong interpretation.

Starch artefact – it may occur due to presence of starch powder with specimen which is present in

the surgical gloves as a lubricant. Starch granules generally are 5-20 mm in diameter & are glassy, refractive, polygonal, PAS positive. They are spore like structure which is misdiagnosed as a nucleus which is either pyknotic or undergoing mitosis. Starch particles appear blue in H & E staining, blue black with Lugol's solution, deep liliac red with PAS. & microscopically reveal maltose cross birefringence under polarized light.
This can be prevented by alternate use of rubber gloves & correct recognition of it in stained section.
Reusable cassettes if not cleaned properly can carry old tissue specimen fragment leading to problem in diagnosis.

Fulgeration/ Heat artefacts –
These artefacts are produced during surgery by electrocautery, laser or chemical used in sterilization of surgical instruments.
Electrocautery used for coagulation of protein, produces excessive heat which in turn causes tissue distortion, it may alter both epithelium & connective tissue. The epithelial cells appear detached & nuclei assume spindled, palisading configuration. There may also separation of epithelium from the basement membrane. Hence these artefacts may render the small biopsy specimen undiagnostic& should be limited to only relatively large specimen.
These artefacts can be avoided by the use of 1. cutting instead of coagulation electrodes. 2. Low milliampere current. 3. Combination of knife & electrical points.

DURING TRANSPORT:
Freezing artefact –
Freezing of biopsy specimen before fixation is not recommended since it causes cytoplasmic condensation secondary to cell dehydration. These are characterized by formation of intracytoplasmic vacuoles which results from ice crystal formation.
10% formalin will freeze at -11^{0}C. Tissue section exhibit 'swiss-cheese' holes in the epithelium & tissue spaces representing area where ice crystals ruptured.
This can be prevented by avoiding freezing before fixation & during transport.

FIXATION ARTEFACTS:
Biopsy followed by the fixation of specimen immediately to prevent tissue from soluble component diffusion thereby interrupt autolysis & putrefaction & to stabilize cell protein. A good fixative agent penetrates the tissue rapidly, preserve cellular details & harden the specimen as a protective measure.
The volume of fixative should be 20 times greater than that of the specimen with thickness not exceeding 6 mm for optimal fixation.
10% neutral buffered formalinis considered as the best fixative. Normally tissues shrink by 33% in formalin & embedded paraffin wax.
Occasionally distilled water & saline can be substituted.
Bizarre appearance of epithelial cells results when specimen submerged in saline for 24 hrs with subsequent fixation in formalin, suggesting malignancy in the specimen.
Such specimen after processing revealed features like large, round, swollen atypical cells with hyperchromatic nuclei, prominent nucleoli, giving an erroneous diagnosis of lymphoma. So if tissue is being sent in saline, it should be immediately placed in 10% neutral formalin solution to prevent misdiagnosis.
Some more fixation artefacts are summerized below.
Ice crystal artefact –
These artefacts produced due to freeze drying method during fexation. Here isopentane is used into which tissue must be plunged 7 immediately cooled at 160^{0}C-180^{0}C with liquid nitrogen. Low temperature is important because unless the whole tissue is frozen, & may lead to disruption artefact by forming large ice crystal. Such artefacts causes total distortion & make the diagnosis difficult. 10% formalin will freeze at -11^{0}C. Tissue section exhibit 'swiss-cheese' holes in epithelium.these artefacts can be avoided by using Lillie AAF, 40% formaldehyde solution.
Shrinkage artefact –
During fixation, tissue shrinks due to
1. Inhibition of respiration
2. Changes in membrane permeability &

3. Change in sodium transport activity.

Delay fixation causes cell shrinkage, cytoplasmic clustering. Farther nuclear chromatin become indistinguishable, nucleoli sometimes not visualized. It shows loss of details of vessels, nerves, glands & impression of scarring & cellularity loss is created. This can be avoided by fixing the specimen immediately in 10% formalin solution as soon as tissue is removed that arrest autolysis & putrefaction by stabilizing cell protein.

Likewise prolong fixation in formalincauses secondary shrinkage & hardening which can lead to separation of tissue & appear as empty spaces in stained section.

Pigmentation artefact –

While fixation of the tissue in the solution containing formalin or mercury, care should be taken to avoid formation of complexes in the tissue which may give rise to pigmentation artefact. Heme from RBS's bind with formalin & form formalin-heme complex that appear as black precipitate in the tissue. This pigment commonly seen in cellular or bloody tissue & autopsy tissue which has no relationship with tissue & can be confirmed by polarised microscopy.These artefact can be prevented by using neutral neutral buffered formalin, & can be removed by treating specimen with picric alcohol or 1% alcoholic solution of sodium hydroxide. Similarly mercury containing fixative show brownish precipitation & tis can be removed by iodine.

Streaming artefact –

These artefacts are caused due to unfixed material diffusion which gives false localization, by coming to rest in places other than their original location. A well known example of these is glycogen.

These artefacts can be prevented by using 1. smaller blocks (reale& Luciano 1970) or 2. strong fixative agent for large bits of specimen.

Diffusion artefact –

These artefacts refer to material may sometimes diffuse out of the tissue. Small molecules like inorganic ions & biogenic amines can be lost from the tissue along with large molecules due to denaturation of associated proteins, chromogenin, in case of adrenalin & nor adrenalin. these can be demonstrated by placing adrenals in iodate. Biogenic amines can be retained by precipitation.

These artefacts can be prevented by proper fixation for accurate localization & also by preventing leaching of ions from the tissue.

Artefacts due to false localization of extraneous material –

These artefacts occur in autoradiography with H3 labelled amino acids, sugars, thymidine &uridine. By the active metabolism, tissue incorporated into these substances giving false localization. This can be removed by washing tissue with cold sodium sulphate & also can be completely avoided by freeze drying.

Artefacts due to chemical changes –

These are brought about by the fixatives like gluteraldehyde. While fixation in it, it will add carbonyl group to the tissue in which they were not present & these group will react with schiff's reagent. These can be prevented by using Bouin's fixation medium for the storage specimens.

Artefacts due to microwave fixation –

The optimal temperature for microwave fixation is recommended is 45-55^{0}C. overheating results in poor section quality whereas overheating produces vacuolization, overstained cytoplasm, pyknotic nuclei.

Microwave brings about denaturation of protein & stabilize the tissue. The microwaves generated by commercial ovens penetrate tissues to a tissue of 10-15 mm thickness.

Artefacts during decalcification –

The tissue surrounding the calcified area will get damaged with knife, so it is better to use saw. Generally decalcification is speeded by application of heat. When it is carried out at 55-60^{0}C, it will result in undue swelling of tissue & completion of digestion. Bone marrow specimen is best fixed in Zenker'sformol solution. After decalcification acid present in the tissues should be neutralized by saturated lithium carbonate or 5-10% aqueous sodium bicarbonate for several hours.

ARTEFACT DURING PROCESSING –

Processing replaces water content of the tissue specimen with supporting medium which provide enough rigidity for the tissue sectioning without damage. 1. Dehydration is the first step in which aqueous fixative fluid remove from the tissue by alcohol.

2. Second step is clearing, which replace dehydrating fluid with fluid miscible with dehydrating fluid & embedding medium.

Too great concentrated alcohol causes rapid removal of water leading to high degree of shrinkage. To prevent this, tissue must dehydrate slowly starting with 50% alcohol.

Prolonged placement of tissue in acetone causes tissue brittle thereby affecting sectioning. Other simple fixatives used to prevent tissue damage are, picric acid, acetic acid, chromic acid etc.

Prolonged immersion of tissue in clearing agent causes tissue to be brittle & obstruct paraffin impregnation. Even a small amount of clearing agent contaminated with wax lead to crumbling & crystallization of tissue during cutting.

Artefacts during tissue processing can be prevented by taking proper care to use adequate amount of clearing agent & no clearing agent left behind to contaminate wax.

Processing floaters or cutting board metastasis –

These are the artefacts in which extraneous material pieces present with small biopsy when 1. While handling biopsy in the laboratory may become adulterated with small fragments of other tissues being processed in same batch. 2. While tissue section being floated out on a water bath they may pick up residual fragments of previous biopsy. These artefacts are avoided by using clean cassettes, cutting boards& instruments.[14]

Artefacts during wax impregnation –

Wax impregnation remove clearing agent from the tissue & permeate it completely to paraffin wax which simultaneously harden to produce block from which sections are cut. Artefact produced is crystallization. Thick tissue absorb more clearing agent & require multiple change of molten wax. To be completely impregnated.

Artefacts due to poor processing –

Inadequate fixation causes extensive loss of tissue architecture also loss clarity within loose connective tissue. These can be caused by faulty tissue processing such as too short processing cycle, inappropriate reagent, exhausted reagent or error in replacing solvent.

Artefacts during embedding –

Incorrect orientation of tissue during embedding are frequently encountered which lead to the important tissue elements being missed or damaged during microtome.

Exposing the specimen for too long during embedding result in excessive hardening & tissue become friable. & form crack during sectioning.

These artefacts can be prevented by correct orientation of specimen in the mould & exposing the specimen to the correct amount of the embedding medium. When multiple specimens are being embedded, do not embed in layer as well as not embed small & large tissue together.

Artefacts during microtome –

Microtome is the means by which tissues are sectioned for microscopic examination. Numerous artefacts result during microtome if proper technique is not followed. Some important ones are summerized below with their ways of prevention.

Artefacts during tissue floating procedure –

Mainly three types of artefacts observed;

1. Air bubbles entrapment – due to poor floatation technique, water bubbles trap under the section & mounting can collapsed after drying bubbles leaving zones which cracks & fails to adhere properly to the slide.

2. Increase temperature of water bath results expansion of tissue beyond limit which shows dark pyknotic nuclei or nuclear bubbling & ‘parched earth’ effect is noted.

3. Floaters artefacts are the tissue appear on the slide that do not belong there. They may be due to previous section bits, or from improper cleaning of cutting surfaces &clearing of water bath. To avoid these problems distilled water rather than tap water should be used & bath should be emptied & dried after each cutting.

Microtomy Artefacts	Causes	Prevention
Ribbon/consecutive sections curved	Edges of block not parallel Dull blade edge Excess wax at one side Tissue varying in consistency	Trim block until edges parallel Replace/sharpen blade Trim away excess wax Re-orient block, cool block with ice, mount individual sections
Alternate thick & thin sections	Too soft wax Loose block or knife Clearance angle insufficiency Faulty microtome mechanism	Cool block with ice, use wax with high melting point Tighten Increase clearance angle slight Check for obvious faults like pawl may be worn
Chatter- thick & thin zones parallel to blade edge	Blade or block loose in holder Excessive tilt of blade Wax/tissues too hard for sectioning Calcified area in the tissue Dull blade	Tighten Replace or use new area of blade Use sharp blade, reduce slant angle of blade, use softening fluid on the tissue Rehydrate & decalcify or surface decalcify Replace blade
Splitting of sections at right angle to knife	Nicks in the blade edge Hard particles in tissue Hard particles in wax	Replace or resharpen the blade, use different area of blade If calcium, then decalcify If minerals, then remove with pointed scalpel Re-embed in fresh filtered wax
Section not form ribbon	Too hard wax Debris on blade edge Incorrect clearance angle	Warm the block surface, use wax with low melting point Clean with xylene Adjust to optimal angle
Section become attached to block on return stroke	Clearance angle insufficient Wax on the blade Debris on block edge Static electrical charge on ribbon	Increase clearance angle Clean with xylene Trim block edge with sharp scalpel Humidify air around microtomy, & place Bunsen burner near blade to ionize the air
Section devoid of tissue area in the block	Incomplete tissue impregnation Wax block detached	Return tissue to vacuum impregnation bath for few hours or reprocess if fault is excessive Reattached with hot spatula
Excess compression of section	Blunt blade Too wide blade bevel Too soft wax	Replace/ sharpen Resharpen to form secondary narrow bends Cool block with ice, use wax with high melting point
Expansion & disintegration of section on water surface	Poor tissue impregnation Too hot water	Return tissue to vacuum impregnation bath for few hours Cool the water
Section rolls in coil instead of flat on blade	Blunt blade Little rake angle Thick section for wax in use	Replace/ sharpen Resharpen to produce shallow cutting angle or reduce blade tilt if clearance angle is large Reduce section thickness or use wax with high melting point

Thick coat adhesive will take stain & background stain may detected leading to irregular, poor quality sections. Mounted unstained sections should be contaminated with dirt, microorganisms, airborne fibers, cellulose fibers.

STAINING ARTEFACTS –

Before staining, residual wax should be completely removed. Blotching of section is caused when section placed in xylene for wax to dissolve. If wax not removed completely, can causes poor penetration of stain leading to area devoid of stain. Also causes subtle effect on nuclear staining producing muddy appearance of nuclei with lack of details. Prolong xylene treatment & restaining will overcome this problem.

Onward, during staining artefacts occur due to old, decomposed dyes, impurities present in dye & leaching of certain substances from tissue into dye which may weak the staining solution. This can be prevented by maintaining ideal temperature & time depending on stain & filtration of staining solution.

ARTEFACTS DURING MOUNTING –

Mounting means for protecting section from getting damage by the application of cover glasses with appropriate mounting media. Artefacts like bubbles are formed under coverslip when mounting medium is too thin & after drying more air get sucked under the edges.

This can be prevented by using adequate thickness of mounting medium & removing air bubbles from under the slide.

ARTIFACTS IN DIAGNOSIS [15]

1. Cholesterol clefts in radicular cysts or periapical granuloma are produced as a result of dissolution of lipids during processing that leave behind needle like spaces.
2. Lacunar cells, the diagnostic clue to nodular sclerosis, a variant of Hodgkin's lymphoma is an artifact induced by formalin fixation and absent with other fixatives. These cells are formed by retraction of cytoplasm towards the nuclear membrane thus giving the appearance of cells enclosed within lacunae.
3. Max Joseph Space (Caspary Joseph Space) associated with lichen planus is an artifactual space in the subepithelial region caused during processing and is attributed to basal cell degeneration.
4. Formalin induced fluorescence can detect melanin pigment in amelanotic melanoma where melanin is not demonstrable in routine hematoxylin and eosin (H and E) section.

CONCLUSION:

Artefacts are encountered in most histopathologic sections which play role in interpretation of diagnosis. Proper processing & preparation of biopsy results in tissue fit for diagnosis. Artefacts inclusion during various process should be reduced or avoided by the the clinicians, assistance, pathologist & histotechnicians. & if artefacts occur & remain unnoticed can create potential diagnostic problems during histopathological examination. The need to recognize these artifacts and attempt to overcome them is the biggest challenge in the histopathology Laboratory. The present review article focused on identifying artifacts, their potential cause and probable ways to overcome them so that misinterpretation can be reduced. Proper handling of specimens and avoidance of faulty techniques will not only reduce artifacts but will help to establish appropriate diagnosis by microscopist.

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