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Imprint and scrape cytology in the diagnosis of gastrointestinal lesions with histopathological correlation

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Abstract

Background: Gastrointestinal lesions are among the commonest causes of morbidity and mortality. Histopathology is a gold standard for the diagnosis of these lesions however, it is time-consuming. Imprint and scrape cytology are techniques of rapid diagnosis which are simple, inexpensive and non-interventional and are an alternative to the frozen section that is expensive and unavailable in many of the peripheral and small centres. They are reported to have high sensitivity and specificity when correlated with histopathology.

Aims & Objectives

1. To study the role of imprint and scrape cytology as a rapid diagnostic tool in the diagnosis of gastrointestinal lesions which are done for diagnostic and therapeutic purposes.
2. To compare imprint and scrape cytology with histopathological diagnosis to know the accuracy, sensitivity and specificity.

Results: Out of 50 cases, 27 cases were neoplastic lesions and 23 were non-neoplastic on histopathology. According to histopathological diagnosis, the majority of malignancies were adenocarcinomas, and the most common site was the colon. The sensitivity of imprint and scrape cytology was 0.898 and the accuracy was 0.880.

Conclusion: Imprint and scrape cytology both can be used reliably for intraoperative or rapid post-operative diagnosis, especially for malignant tumors. Its utility is limited in the case of non-neoplastic or inflammatory conditions.

Keywords Histopathology, Imprint cytology; Gastrointestinal lesions; Scrape cytology

Introduction

Cytological diagnosis is a very important adjunct to histological diagnosis.[1] The imprint and scrape cytology samples can be taken from freshly resected surgical specimens or biopsies. [2] The report is available

in a very short duration which can help a surgeon intraoperatively to make a decision. The cellularity of these smears is adequate for neoplastic lesions and the morphology of the cells is well preserved. It is an affordable diagnostic tool available to smaller setups.

Worldwide, gastrointestinal cancers are the second most common type, while tuberculosis and other infective lesions are a source of morbidity and mortality, especially in developing countries like India.[3] The present study was undertaken to establish the role of imprint and scrape cytology for diagnosing and studying various gastrointestinal tract lesions including non-neoplastic, neoplastic and malignant lesions, compared with the final histopathology diagnosis in gastrointestinal tract lesions.

Materials and methods

This was a prospective study of gastrointestinal lesions conducted at the department of pathology in a tertiary care hospital, over a period of 24 months, from October 2018 till October 2020. A total of 50 cases were studied.

Inclusion criteria:

1. All the resected specimens of gastrointestinal tract lesions including non-neoplastic, infective, benign and malignant tumors were included.
2. Metastatic tumors to the Gastrointestinal tract were also included.

Exclusion criteria

1. Endoscopic biopsies were excluded.
2. Inadequate / necrotic /autolyzed samples.

All the freshly operated gastrointestinal specimens were sent to the histopathology section of the Department of Pathology in a 10% neutrally buffered formalin jar. They were immediately examined for gross features and the clinical details were noted simultaneously. The surface of the specimen was dabbed gently by filter paper to remove the excess blood or exudate and a fresh cut was taken by a scalpel. Imprint and scrape smears were taken from the freshly cut surface before their fixation. The imprint was done by placing a clean glass slide (touch imprint), labelled by diamond marking pencil with a specific cytology number, on the fresh specimen without any gliding movement.

Similarly, scrape smears were made by scraping the lesion with the help of a glass slide edge or a scalpel. The material collected was placed on one end of the slide and pressed by another slide. It is then spread in the opposite direction followed by immediate fixation. Minimum 2 to 3 slides of imprint and scrape cytology smears were made respectively. The smears were fixed in 95% ethyl alcohol and stained with Rapid Papanicolaou stain and Rapid Hematoxylin and Eosin (H & E) staining techniques.

The stained imprint and scrape smears were then studied on light microscopy and the cytological diagnosis was given. The procedure took around 10 to 15 minutes. The same tissue was then processed by routine standard histopathological technique and a final diagnosis was given.

The findings of imprint cytology, scrape cytology and histopathology were noted and correlated as per the study proforma. The final results were entered in a master chart. The data was noted, and statistical analysis was done.

Results

This prospective study was carried out with a total number of 50 patients to study the imprint and scrape cytology findings in the resected specimens of the gastrointestinal tract and correlate their results with the final histopathological diagnoses.

Table 1: Age distribution of lesions

AGE	0-10 years	10-20 years	20-30 years	30-40 years	40-50years	50-60years	60-70 years	70-80 years
No. of cases (N=50)	5(10%)	2(4%)	7(14%)	5(10%)	4(8%)	10(20%)	9(18%)	8(16%)

The maximum number of cases seen in the age group of 50-60 years and least was seen in 10-20 years of age. Out of a total of 50 cases, 31 cases (62%) were seen in males and 19 (38%) were females. The male to female ratio was 1.65:1. Maximum cases were found in the colon (58%), followed by the small intestine (30%) and least was seen in the stomach (12%).

Table 2: Types of malignancies seen in the gastrointestinal tract according to histopathological diagnosis

Types of malignancies	**Number of cases**
1. Adenocarcinoma	20 (77%)
2. Squamous cell carcinoma	4(15%)
3. Metastases from the ovary to colon	1(4%)
4. Non- Hodgkin lymphoma of the colon	1(4%)
Total	**26**

A maximum number of cases comprised of Adenocarcinoma (77%) followed by squamous cell carcinoma (15%); metastases from the ovary to the colon (4%) and non-Hodgkin lymphoma (4%) comprised if one case in our study. Out of 20 cases of adenocarcinoma, 12 were in the colon, 4 were in the small intestine and 4 were in the stomach. Out of 4 cases of squamous cell carcinoma 3 cases were from the stomach and 1 case was from the rectum.

The gastrointestinal tract lesions are categorized in decreasing order of frequency as follows: The highest number of cases are of the neoplastic lesions (54%) which included 26 malignant tumors and 1 benign tumor followed by inflammatory lesions (38%) and the least number is miscellaneous (8%) category which includes fat necrosis, Hirschsprung's disease, angiodysplasia and lymphangioma of mesentery of colon (8%).

Table 3: Cytology and histopathology diagnosis of GIT lesions.

Imprint and Scrape cytology diagnosis	Histopathology diagnosis	Neoplastic	Non-neoplastic & inflammatory	Total
1.Necro-inflammatory lesion	Fat necrosis		1	1
2.Chronic inflammatory lesion. No evidence of granuloma.	Crohn`s disease		1	1
3.Suspicious of lymphoma cells.	Non-Hodgkin lymphoma	1		1
4. No opinion possible.	Vascular anomaly possibly Angiodysplasia (Angi ectasia)		1	1
5.Inflammatory lesion	Perforation peritonitis		5	5
6.Necro-inflammatory lesion.	Gangrenous intestine		3	3
7.No opinion possible	Hirschsprung`s disease		1	1
8. Suspicious of malignant GIST.	GIST of low malignant potential	1		1
9. Adenocarcinoma	Adenocarcinoma	20		20
10. Suggestive of tuberculosis	Tuberculosis		8	8
11.Chronic inflammatory lesion	Intestinal perforation secondary to ascaris lumbricoides with granulomatous inflammation		1	1

12.No opinion possible	Metastases of endometrioid carcinoma ovary to colon	1		1
13.Squamous cell carcinoma	Squamous cell carcinoma	4		4
14. No opinion possible	Lymphangioma of the mesentery		1	1
15. Chronic inflammatory lesion	organizing inflammatory lesion with foreign body giant cell reaction		1	1
	Grand Total	27	23	50

Out of the total of 50 cases, 27 cases were neoplastic and 23 cases were diagnosed as non-neoplastic on histopathology. The cytological diagnosis of 'No opinion possible' showed only normal intestinal mucosal cells in the smears but on histopathology showed varied diagnosis like angiodysplasia of colon, Hirschsprung`s disease, metastases of endometrioid carcinoma ovary to colon and lymphangioma of mesentery of colon

The order of presentation of symptoms, the most common symptom observed in this study was a pain in the abdomen (70%), followed by an intestinal obstruction (56%), a lump in the abdomen (46%), bleeding per rectum (32%), weight loss (32%), diarrhea (22%), vomiting (18%) and the least common symptom was fever (12%).

The miscellaneous conditions include fat necrosis, GIST, intestinal gangrene, perforated bowel, Hirschsprung`s disease, angiodysplasia and lymphangioma of mesentery of colon.

Table 4: Results of Cytology (Imprint/Scrape) Vs HPE

Test	Positive	Negative	Total
Disease +	44	5	49
Disease -	1	0	1
Total	44	6	50

Imprint and scrape cytology findings showed that 49 cases were suggestive of gastrointestinal tract lesions out of the total 50 cases. Among them, the cytology diagnosis of 44 cases correlated with the histopathology diagnosis. While 5 cases were false negative on cytology which either showed only normal mucosal cells and or inflammatory cells, therefore definitive diagnosis could not be made. On histopathology, these were diagnosed as Crohn`s disease, metastases from ovary to colon, angiodysplasia, Hirschsprung`s disease and lymphangioma of mesentery of colon.

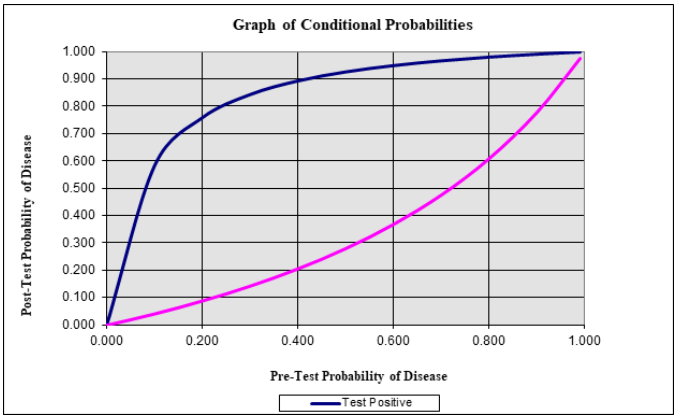
Out of the total 50 cases, 1 case was false positive on cytology. This case was diagnosed as suspicious of malignant GIST on cytology, based on high cellularity and number of mitoses. However, on histopathology, it was diagnosed as GIST of low malignant potential.

Table 5: Sensitivity and specificity of Imprint Vs HPE

Calculated Diagnostic Accuracy Parameters:				
Sample size =	50			
Prevalence =	0.980		Lower limit	Upper limit
Sensitivity =	0.898	95% CI(Sens) =	0.813	0.983
Specificity =	0.000	95% CI(Spec) =	0.000	0.000
Accuracy=	0.880			
PPV =	0.978			
NPV =	0.000			

The true negative parameter was zero in our study therefore, specificity in this study cannot be calculated.

Chart 1: Conditional probabilities for Imprint cytology.



Discussion

Cytologic sampling may be the sole specimen collected in very narrow areas of the intestinal tract (ducts and strictures), in subepithelial, submucosal and mural mass lesions and in endoscopic sampling of extraintestinal tissues.[4]

Although frozen section analysis is a preferred method of intra-operative consultation, the determination of the accuracy of cytology in the intraoperative diagnosis of a tumors and in resource-limited setups is essential and has been compared with the gold standard technique of histopathology.[5] The use of either frozen section or cytological examination alone has an acceptable rate (93–97%) of correct diagnosis, with regard to interpretation of benign versus malignant.[6] If the lesion is malignant, widespread dissection including lymph nodes can be done simultaneously during the same surgery and thus preventing the need for a second surgery. The pathologist's primary task is to differentiate and classify the lesions of native tissue that can be accomplished by cytomorphologic criteria and with judicious use of ancillary studies.[7]

The present study was conducted over a period of 2 years to assess the utility of imprint and scrape cytology in the diagnosis of gastrointestinal cases which included a total of 50 cases.

Table 6: Comparison of age range and most common age group of all the cases with various other studies.

Authors and reference number	Age ranges	Most common age group
Negi et al [6]	1-95 years	5th decade
Pandey et al [8]	5 days – 78 years	2nd decade
Ranga Swamy et al [9]	16- 83 years	5th decade
Sayeed et al [10]	3-82 years	2nd to 4th decade
M vij[11]	26-76 years	---
Present study	5 months – 80 years	5th decade

In the present study, the age ranged from 5 months to 80 years of age similar to the other studies like Negi et al, Pandey et al, Ranga Swamy et al, Sayeed et al, M vij. [6-11] The maximum number of cases were (10 cases) seen in the age group of 50-60 years of age.

In our study, the most common age group was the 5th decade like the studies mentioned in the table. [6-10]

Table 7: Comparison of sex ratio of the gastrointestinal lesions with other studies

Authors and reference number	Number of males	Number of females	Sex ratio
Negi et al [6]	128 (64%)	72 (36%)	1.78:1
Pandey et al [8]	67 (64%)	38 (36%)	1.76:1
Ranga Swamy et al [9]	68 (63%)	39 (36%)	1.74:1
Sayeed et al [10]	217 (62%)	133 (38%)	1.63:1
M vij et al [11]	20 (74%)	7 (26 %)	2.67:1
Present study	31 (62%)	19(38%)	1.65:1

In the present study, 31 (62%) cases were males and 19 (38%) cases were females. M:F ratio was 1.65:1. The sex ratio of our study was comparable with the studies mentioned (table 7) except for the study by M vij that showed a higher sex ratio of 2.67:1.[11]

Table 8: Comparison of the most common site of gastrointestinal lesions with various other studies.

Authors and reference number	Most common site
Negi et al [6]	Colon (49%)
Pandey et al [8]	Colon (100%)
Ranga Swamy et al [9]	Colon (100%)
Sayeed et al [10]	Rectum and anal canal (63%)
Present study	Colon (58%)

In the present study, the most common site of the gastrointestinal lesion was the colon 29 (58%) cases followed by ileum and duodenum 15 (30%) cases and the least number of cases was seen in the stomach that is 6 (12%) cases. Similarly, in the study conducted by Negi et al the most frequent site was also colon 98 cases (49%) followed by rectum and anal canal 66 (33%) and caecum 23 (11.5%) and rectum and colon 13 (6.5%).[6] Whereas, in the study conducted by Sayeed et al the commonest site was rectum and anal canal 121 (63%) cases followed by colon 63 (33%) and caecum 7 (4%).[10] Pandey et al and Ranga Swamy et al only reported samples taken from colon. [8, 9]

Table 9: Comparison of the most common clinical presentation of gastrointestinal lesions with various other studies

Authors and reference number	Most common clinical presentation
Negi et al [6]	Bleeding per rectum (47.5%)
Pandey et al [8]	Diarrhoea (55%)
Ranga Swamy et al [9]	Diarrhoea (66.36%)
Sayeed et al [10]	Bleeding per rectum (32.53%)
Ritesh et al [12]	Bleeding per rectum (69.68%)
Present study	Abdominal pain (70%)

In our study, abdominal pain (70%) was the most common clinical presentation followed by, intestinal obstruction (56%), a lump in the abdomen (46%), bleeding per rectum (32%), weight loss (32%), diarrhea (22%), vomiting (18%) and lastly fever (12%).In other studies, the most common clinical presentation was as mentioned in Table 9.

Table 10: Comparison of histopathological diagnosis of gastrointestinal lesions with various other studies

Authors and reference number	Neoplastic	% Of Adenocarcinoma colon	Non-neoplastic
Negi et al [6]	48%	(86%)	52%
Pandey et al [8]	73%	(82%)	24%
Ranga Swamyet al [9]	23.37%	(94.12%)	76.63
Sayeed et al [10]	6.2%		93.8%
Ritesh et al [12]	62.09%	(89.71%)	30.65%
Sachin Kolte et al[5]	---	(50%)	---
Present study	54%	(77%)	46%

In the present study, majority of lesions were neoplastic that is 27 (54%) and 23 (46%) were non-neoplastic, similar to the studies by Pandey et al (73%) and Ritesh et al (62.09%). [8,12] In contrast, the studies by Negi et al (52%), Ranga Swamy et al (76.63%), Sayeed et al (93.8%), mentioned higher number of non-neoplastic lesions compared to neoplastic lesions. [6,9,10]

In our study out of 27 neoplastic lesions, 26 (52%) were malignant and 1 lesion was benign (3.7%). In a study by Ranga Swamy et al, among the neoplastic lesions, 32 % were benign and 68% are malignant. [9]

In our study, out of the total 26 malignancies, the highest number of cases were of adenocarcinoma 20 cases (77%), followed by 4 cases (16%) of squamous cell carcinoma, 1 case (4%) of metastases of the ovary to colon and 1 case (4%) of non-Hodgkin lymphoma of the colon. The studies conducted by Pandey et al, Negi et al, Ranga Swamy et al, Ritesh et al also showed that adenocarcinoma as the commonest type of malignancy which was comparable with our study. [6, 8, 9, 12]

In a study by Sachin Kolte et al out of total of 8 gastrointestinal cases, 4 cases (50%) were diagnosed as adenocarcinoma and were the highest in number. [5]

Cytology smears of adenocarcinoma in our study showed crowded and Di cohesive three-dimensional clusters of tumor cells with loss of polarity, elongated hyperchromatic nuclei with high N:C ratio and moderate cytoplasm. A study by Conrad et al showed similar pattern with branching papillary fragments and micro acinar areas in disorderly arrangement. Round tumor cells with oval nuclei, many single cells and prominent "dirty" tumor diathesis were noted. [7]

In present study, 23 cases were reported as non-neoplastic on cytology that were reported on histopathology as tuberculosis (16%), fat necrosis (2%), Crohn`s disease (2%), Hirschsprung`s disease (2%), angiodysplasia (2%), lymphangioma mesentery (2%), gangrenous bowel (8%) and perforative lesion of intestine (12%). In the study by Negi et al, non-neoplastic lesions included Non-Specific Colitis 28 %, Inflammatory Bowel Diseases 26 %, Benign Polyp 15%, Granulomatous Colitis 7 %, Granulomatous Colitis possibility of Tuberculosis 6 %, Microscopic Colitis 1 %, Inconclusive 17 %.[6]

Our study reported 5 (10%) false negative cases and 1 (2%) false positive case on cytology whereas, the study by Negi et al showed 2 (1%) false negative and no false positive cases. [6]

False positive

Among the 27 neoplastic cases, 1 case on cytology was diagnosed to be malignant GIST due to the atypical features of spindle cells and the number of mitoses. On histopathology, it was diagnosed as GIST with low malignant potential. Hence was considered to be false positive case. Our study included only one case of GIST in a 73 yr old female with primary GIST in the stomach.

Malignant and metastatic lesions were commonly highly cellular in the study by M Vij.[11] We did not have any mode of comparison for the cellularity in our study as we had only 1 case of GIST. In our study, smears studied showed predominantly spindle cells, arranged in cohesive to lose three-dimensional clusters and dispersed singly. Tumor cells formed fascicles with a parallel arrangement of nuclei along with streaming. The tumor cells had, ovoid to elongated nuclei with fine granular chromatin. The cytoplasm was fibrillary with many cytoplasmic extensions. Mitoses was also noted. The stroma was fibrillary and loose with focal necrosis. The findings were similar to the study by M Vij and Richardson et al. [11 ,13]

The criteria for differentiation of benign from malignant GIST remain controversial. Many parameters have been proposed, tumor size and proliferative activity have been found to be the most important prognostic indicators. [14,15] In our study, histopathology sections of GIST were studied that showed features of the gist of low malignant potential as the size of the tumor was 4x4x3cm which is >2 and <5cm and mitosis ≤5 per 50 hpf. Cytology smears showed nuclear pleomorphism, mitosis and focal necrosis that suggested diagnosis to be in favour of

malignant GIST. In the study conducted by Negi et al, there were no false positives.[6]

The differential diagnosis between GISTs and gastrointestinal leiomyomas is difficult due to their overlapping clinical and cytologic features. Leiomyoma shows varying cellularity and are composed of bland spindle cells with abundant cytoplasm often having a fibrillary appearance.[16]

False negative

In our study there were 5 false negative cases including Crohn`s disease, metastases of the ovary to the colon, angiodysplasia of the colon, lymphangioma of the mesentery of colon and Hirschsprung`s disease of the colon. The cytology of Crohn`s disease of the colon only showed scattered fibrocytes with chronic inflammatory cell infiltrate. Our study included only 1 case of Crohn`s disease, whereas Ranga Swamy et al had 2 cases (2.44%).[9]

In case of metastases of the ovary to the colon, the cancer diagnosis was missed due to scant cellularity. In the case of angiodysplasia, no endothelial cells or hemorrhagic background was noted. In the case of lymphangioma, no endothelial cells or lymphatic fluid was seen. Hirschsprung's disease of the colon showed only normal intestinal cells. Hence the diagnosis was missed on cytology.

Our study had only 1 case of Hirschsprung`s disease. In the study by Pandey et al, had 6 cases (7.59%) of Hirschsprung`s disease and suction biopsy sampling of mucosa and submucosa was considered the method of choice for diagnosis of Hirschsprung`s disease.[8] A study by Ritesh et al had 3 cases (7.89%) of Hirschsprung`s disease. [12]

No diagnostic cellularity can be found in lesions like Hirschsprung`s disease, angiodysplasia or lymphangioma colon. An extensive literature search didn't reveal a comparative cytological study of these lesions. This is a known limitation of cytology.

In the study by Negi et AL, all 57 cases reported as malignant on cytology proved to be malignant on biopsy. Among those 2 cases were diagnosed as false negative which were also due to scant cellularity of the sample like our study.[6]

There was no literature available for comparison of positive predictive value, negative predictive value and accuracy of our study with other studies.

Table 11: Comparison of sensitivity with various studies

Authors and reference number	Sensitivity
Negi et al [6]	96.6 %
Sharma et al [17]	98.5%
Geramizadeh et al [18]	88%
Brouwer et al [19]	88.2%
Present study	89.8%

The present study showed sensitivity as 0.898 (89.8%) which was compared with the other studies in table 11. [17-19]

The accuracy of our study was 88 %; whereas Rakesh Meher et al and Sachin Kolte et al showed an accuracy of 87.5% and 97.3% respectively. [5, 20]

Tuberculosis

In our study, there were total 8 cases which were diagnosed as tuberculosis on cytology and were confirmed on histopathology. A study by Ritesh et al and Ranga Swamy et al showed 2 (5.26) and 6 cases (7.32%) tuberculosis lesions respectively. [9, 12]

These were characterized by presence of confluent granulomas with areas of caseation necrosis, aggregation of epithelioid cells, Langhans giant cells and lymphocytic infiltrate. A study by Sayeed et al had 3 cases (0.90%) of ileocaecal tuberculosis.[10] A study by

Sachin Kolte, included 2 cases (2.6%) of intestinal tuberculosis.[5] A study by Das and Pant mentioned 23 cases (29 %) of intestinal tuberculosis.[21]

Fat necrosis

Our study included only one case of fat necrosis which was diagnosed as chronic inflammatory lesion on cytology. In the study by Vikas et al one case of fat necrosis within a subcutaneous lipoma in the anterior abdominal wall which on cytology was diagnosed as lipoma and later as fat necrosis on histopathology.[22]

Non-Hodgkin lymphoma:

Our study included only 1 case of primary non-Hodgkin lymphoma of the colon. Cytologically there were dispersed monotonous lymphoid cells with scant cytoplasm and many lymphoglandular bodies. Similar findings were noted in Conrad et al. [7]A study by Ritesh et al had 2 cases (2.94%) of the large cell type of non-Hodgkin's lymphoma. [12] Another study by Sachin Kolte included 1 case (1.3%) of lymphoma. [5]

Squamous cell carcinoma

Our study included only 1 case in the rectum and 3 cases of squamous cell carcinoma in the stomach. In a study by Ritesh et al there were 5 cases (55.56%) of squamous cell carcinoma of the anal canal. [12] In another study by Negi et al 1 case (1%) of squamous cell carcinoma of colon was noted, similar to our case. [6] A study by Sachin Kolte included 1 (1.3%) case of squamous cell carcinma of the esophagus. [5]

Metastases to colon

In our study, there was only 1 case of endometrioid carcinoma metastases from the ovary to the colon. A study by Ritesh et al showed 2 cases of metastases to the large bowel (5.88%).[12]

In our study imprint and scrape cytology was the method used and was confirmed on histopathology sections of the resected gastrointestinal specimen. Similarly, a study by Kolte et al used intraoperative scrape cytology.[5] In contrast, a study by Negi et al used intraoperative imprint and brush cytology as the method of choice with biopsy as a confirmatory test. [6] In a study by M vij et al, Fine needle aspiration cytology (FNAC) was performed using a 22-gauge needle attached to a 10 mL disposable syringe under ultrasound guidance of intra-abdominal tumors. [11]

In a study by M Vij et al cytology was reviewed in all cases with emphasis on the following cytological features: Overall cellularity, smear pattern (cohesion vs. dispersed cells), palisading, crush artifact, prominent vascular pattern, spindle versus epithelioid cell morphology, nuclear grooves and inclusions, nuclear pleomorphism, presence of nucleoli, round or blunt-ended oval or wavy nuclei, multinucleation/bizarre cells/or giant cells, perinuclear vacuoles, cytoplasmic quality, mitoses and necrosis; similar to our study. [11]

Conclusion

The gastrointestinal tract is one of the most common sites for non-neoplastic as well as neoplastic lesions. Early diagnosis of resected specimens is important especially in cases of malignancy and therefore imprint and scrape cytology plays a crucial role as an adjunct to histopathology.

Neoplastic gastrointestinal lesions displayed a better correlation of cytological smears with histopathology diagnosis in comparison to non-neoplastic lesions. Therefore, while interpreting non-neoplastic or inflammatory conditions caution should be exercised as some of these lesions are better appreciated only on histopathology.

It is essential to correlate history, clinical findings, investigations and gross findings while interpreting

cytology smears to avoid false negative and false positive diagnosis.

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