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EVALUATION OF MALIGNANT BILIARY TRACT STRICTURES WITH ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY GUIDED BRUSH CYTOLOGY

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Abstract:

Introduction: The gold standard method for evaluating biliary tract lesions is endoscopic retrograde cholangiopancreatography (ERCP). The patient who has a benign condition must not undergo extensive surgery in order to receive a prompt diagnosis. In our system, obstructive jaundice is frequently caused by restrictions brought on by malignancy. In these situations, stenting or papillotomy are used to release the block by performing an ERCP operation. Biliary strictures that are thought to be cancerous but lack a tissue diagnosis, or "indeterminate strictures," frequently present diagnostic challenges. To determine the next step in the management procedure, pathological confirmation is preferred. The diagnosis of biliary tract lesions is made safe and accurately by brush cytology.

Materials and method: The research was conducted prospectively over a year. 40 cases of malignant strictures with obstructive jaundice who underwent ERCP for diagnosis and therapy were collected for cytological study. To determine mild basal cytomorphology, five examples of benign stricture were examined. These smears were produced and examined for typical cytological characteristics.

Results: A prolonged follow-up was found 28 of the 38 occurrences involved cancer, five had reactive responses, and five had NOS-suspicious results. 20% of the specimens included gall bladder cancer, 12.5% contained periampullary cancer, and 5% contained pancreatic ductal adenocarcinoma at examination. Pancreatic ductal adenocarcinoma was detected by cytology with a detection rate of 100%, cholangiocarcinoma by 85.7%, periampullary carcinoma by 80%, and gall bladder carcinoma by 58.3%. In general, brush cytology was 73.6% sensitive. Indicators of malignancy included increasing cellularity, reduced polarity, nuclear hyperchromasia, aberrant nuclear shape, and nucleolar importance in the cytomorphological analysis.

Additional criteria for the cancer diagnosis were nuclear variation, background abnormal cells, and multinucleated cells.d a total of six more instances.

Conclusions: The current investigation provides evidence that ERCP-guided brushing, When assessing instances of malignant biliary tract strictures, cytology is a sensitive approach.

INTRODUCTION:

During endoscopic retrograde cholangiopancreatography (ERCP) on patients with jaundice, many biliary strictures are found to be malignant. Malignancy is frequently not confirmed histologically, though. Uncertainty over the diagnosis makes it impossible to make rational judgements about therapy, and it seriously impairs the quality of information given to the patient about their prognosis.[1]

In India, biliary lesions encountered in clinical practise frequently appear with obstructive jaundice. Both extrahepatic and intrahepatic sources are possible. A bile duct stricture, stone, or malignancy are frequently the causes of extrahepatic cholestasis, which is characterised by dilated bile ducts [2]. The majority of the Northern Indian literature published there is very unequivocal in demonstrating that the majority of patients coming in large setups have malignant lesions as the source of obstructive jaundice [3]. Malignant lesions are reported to occur between 63.3% and 75% more frequently than benign instances [3-5]. A diagnostic or therapeutic ERCP is performed in the majority of these instances. The gold standard for evaluating the extrahepatic bile duct is still direct imaging via ERCP.

The degree of biliary dilatation, the existence or absence of a mass in the head of the pancreas, and the detection of metastatic disease can all be determined using non-invasive radiological techniques such as ultrasound, computed tomography (CT), and magnetic resonance imaging.

Except when used to assist percutaneous biopsy or percutaneous fine needle aspiration, these procedures have the drawback of being unable to make a definitive histological diagnosis. The chances of spreading an early cancer are high with percutaneous sampling procedures. [6,7]

The current study stresses the need of performing brush cytology during the ERCP treatment, which is mistakenly carried out in the majority of cases of malignant biliary stricture, in order to spare the patient from having to undergo any additional procedures for tumour diagnosis and subtyping. Additionally, if precise cytological criteria and the right smearing method are followed, the procedure's sensitivity can be boosted.

MATERIALS AND METHODS:

Study sample: For this prospective study, which was conducted over a year, we assessed 40 patients who visited the Aasav Hospital, Muzaffarpur, India. The study comprised patients who had signs and symptoms of obstructive jaundice (caused by biliary strictures) and clinical suspicion of cancer.

Malignancy was diagnosed and confirmed using clinical and radiological examinations, clinical disease progression, histopathology, and fine needle aspiration cytology.

Methods: Clinical evaluations of the patients were conducted, and their demographic information was logged. Each case's clinical and biochemical data, including a thorough clinical history and a liver function test, was accurately documented. Findings from radiological tests such as computed tomography, ultrasonography, and cholangiograms were also documented. ERCP was carried out utilising a common video duodenoscope. Using a papillotome introduced using an insertion wire, endoscopic sphincterectomy was carried out after the ampulla was visualised. Bile duct strictures were localised using contrast fluid and radiological assistance. A double lumen brush was used to rapidly travel back and forth over the strictures. The treatment was carried out by a skilled gastrosurgeon following stringent aseptic guidelines and with the patient's informed written consent. All of the study participants allowed for the collection of sufficient brush cytology samples. In the endoscopy operation room, a skilled pathologist prepared cytosmears.

Five smears were made and stained with quick Papanicolaou (2 smears), haematoxylin and eosin (2 smears), and the stain Giemsa (1 smear) using cellular material that had adhered to the brush. A

thorough cytological analysis was performed and reported. Software SPSS 23 was used to conduct the statistical analysis.

Evaluation of cytomorphology: Detailed cytological properties were examined in cytological smears. The following morphological characteristics were evaluated: (1) cellularity; (2) background; (3) arrangement of cell distribution; (4) nuclear to cytoplasmic ratio (5) nuclear size; (6) polarity; (7) nuclear outline; (8) nuclear shape; (9) nuclear variation > (x2 or x4); (10) amount of cytoplasm; (11) mitosis; (12) chromatin and (14) multinucleate cell. Studies were also conducted on additional cytological characteristics like nuclear grooves, convolutions, notches, moulds, and necrosis. Its nuclear size was nuclear variant was likened to a harmless glandular cell from harmless smears, and size was identical to that of an RBC. When the ratio was larger than 2:1 or the nucleus made up more than 50% of the total volume of the cell, it was noted that the nuclear cytoplasmic ratio was enhanced. A third pathologist was consulted in the event of a disagreement after two independent pathologists reviewed the samples. The smears were grouped into harmless, reactive, tumours, and not Otherwise Specified (NOS)-suspicious categories. NOS-suspicious streaks were viewed as positive for the purposes of the analysis, while reactive streaks were viewed as negative. Clinical and radiological monitoring of the patients was done. Along with association with the epidemiological and cytological characteristics, the diagnostic sensitivity of the bristle cytology process was evaluated. According to the following formula, the method's sensitivity was determined: sensitivity=true positive cases/(true positive+false negative) x100.

RESULTS:

During the course of the investigation, transpapillary brush cytology was performed on a total of 38 cancer cases. The patients were a median age of 54. The M:F ratio was 1: 2.1, with 12 males and 26 females. Clinical follow-up and radiography verified the rest. In our cases, gallbladder cancer was the most frequent kind of malignancy (61.5%), followed by cholangiocarcinoma (22%), periampullary cancer (11.5%), and pancreatic carcinoma (6%), in that order. There was histological evidence of cancer in 23 of 38 patients. Gall bladder USG assisted aspiration cytology also became available and was positive for cancerous cells in 19/23 cases of cancer.

The average serum bilirubin concentration and average alkaline phosphate concentration for the biochemical analyses, respectively, were 11.32 mg/dL and 1595 IU/L, respectively. The values were in line with the jaundice with obstruction laboratory criteria. While undergoing the surgery, the patents experienced no difficulties.

Biliary brush cytology: Only 5% of the cases sampled by biliary brush had insufficient cellular material for interpretation in the first brushings, which represented 95% of the cases. Since sufficient samples were taken from them and there was a significant radiological and clinical suspicion of cancer, the operation was repeated.

The cytological smears were divided into four categories: malignant, reactive, NOS suspicious, and benign. During the course of the disease, one case was sampled three times; the first two smear results showed reactive cytology, and the final smear resulted in malignant tissue. The last diagnosis was taken into account. The treatment was repeated since the patient's clinical condition was declining and the tumor's radiological size was growing.

Eight cytological samples from 38 cases of cancer were labelled harmless, five as receptive, five as NOS-suspicious, and 28 as cancer. NOS-suspicious streaks were regarded as positive for purposes of analysis, while responsive streaks were seen as negative. Brush cytology had a diagnostic sensitivity of 73.6 (28/38); it correctly identified 100% of pancreatic ductal adenocarcinomas (1/1), 85.7% of

cholangiocarcinomas (6/7), 80% of periampullary cancer cases, and 58.3% of cases of cancer gall bladder (14/24) [Table 1]

Table 1: Biliary brush cytology sensitivity

Clinical diagnosis	Number of cases	Detected	Not detected	Sensitivity (%)
Carcinoma gall bladder	24	14	10	58.3
Pancreatic carcinoma	1	1	0	100
Cholangiocarcinoma	7	6	1	85.7
Periampullary carcinoma	6	4	2	66.6
Total	38	28	10	73.6

The benign smears had proper nuclear to cytoplasmic ratios, sufficient cytoplasm, and modest levels of cellularity with cells arranged in monolayer sheets of typical round epithelial cells. It was impossible to see any big or unusual cells, mitosis, or necrosis. Haemorrhage and acute inflammation were present in the background of reactive smears, which exhibited a moderate to high cellularity. An overview of the cells in each smear provide in Table 2.

Table 2: Detailed cytological feature evaluation in each cytological category.

	Benign smear (n=9)	n=9	Reactive smear (n=4)	n=4	Malignant (n=21)	n=21	NOS-suspicious (n=6)	n=6
Cytological features	Category							
Necrosis	Absent	9	Absent	4	Present	17	Absent	6
Cellularity	Low	9	Moderate High	3 1	Moderate High	9 12	Moderate High	4 2
Mitosis	Absent	9	Absent	4	Present	5	Present	5
Background	Haemorrhage that is faint and clear	9	Hemorrhage Acute inflammation	4 2	Hemorrhage Acute inflammation	13 8	Hemorrhage Acute inflammation	5 1
Giant cells	Absent	9	Absent	4	Present	8	Absent	6
Cell disposed in	Monolayer sheets(1-3) Benign columnar cells Cluster of <5 cells	9 9 9	Sheets(>5) clusters	4 4	Sheets(>5) Clusters Pseudopapillae Acini formation	16 18 7 8	Sheets(>5) Clusters Pseudopapillae Acini formation	3 2 2 2
Background atypical cells	Absent	9	Absent	4	Present	9	Present	3
Polarity	Maintained	9	Maintained	3	Lost	18	Maintained	4
Cytoplasm	Pale eosinophilic	9	Pale eosinophilic	4	Moderate Scant	10 12	Moderate	5
Nuclear size	>1.5 RBC size	0	>1.5 RBC size	0	>1.5 size of RBC	18	>1.5 size of RBC	5
Nucleoli	Absent	9	Absent	4	Present	22	Present occasionally	5
Nuclear to cytoplasmic ratio	Normal	9	Normal	3	Increased	19	Increased	4
Chromatin	Fine	9	Fine	4	Hyperchromatic	13	Clumped	5
Shape	Oval to round	9	Oval to round	4	Oval to round Angulated Grooving Moulding	5 11 5 4	Oval to round to elongated	5
Variation	Absent	9	<(x2)	4	>(x2) >(x4)	11 13	Between (x2-3)	6
Margins	Regular	9	Regular	4	Irregular	20	Irregular	4

With bleeding and severe inflammation in the backdrop, reactive streaks displayed an average to high cellularity. Moderate pleomorphism, nuclear overcrowding and cell arrangement in layers and clustered were all present. The cancer smears were mildly to highly cellular, with background haemorrhage and acute inflammatory responses. Layers of cells had been disposed of and aggregates with the development of acini and pseudopapillae. With an increase in nuclear cytoplasmic ratio, polarity was lost. Round to oval in shape, some of the cancerous cells were spindled. RBCs had nuclei larger than 1.5. Five of the cancerous smears revealed reactive clusters of cells. In 18/22 cancerous smears, necrosis was visible. Five instances' worth of cytomorphology showed smears to be somewhere between sensitive and cancerous. They were deemed to be NOS-suspicious. Cells were arranged in layers and clusters within the cellular streaks. Although there was nuclear clustering, the nuclear membrane was normal, and the nuclear variability ranged from x2 to x3, with nucleolar prominence in one example. There was no mitosis, and multinucleate cells could be detected. Background substantial inflammation was present in 4/22 cancer smears.

DISCUSSION:

Malignant biliary strictures are difficult to diagnose early. When palliative care, such as stenting, is the basis of treatment, the majority of patients arrive late. The malignancy is typically curative surgery is not an option for patients with locally advanced cancer, whether or not there are distant tumours. Even so, to properly plan chemotherapy for both resectable and non-resectable cancers, a correct tissue diagnosis is required [8].

Since biliary and pancreatic duct lesions are not always easily accessible for biopsy, cytological methods have frequently replaced traditional diagnostic methods [9,10].

Percutaneous radially assisted fine needle aspiration is one of the most accurate methods of diagnosis for pancreatobiliary cancers, although it requires a clearly defined mass lesion for optimal samples. Due to poor cellular conservation, other techniques such as bile, pancreatic, and intestinal fluid discharges have low specificity and sensitivity [11]. The favoured initial approach of diagnosis in many patients with pancreatico-biliary limitations is now brush cytology carried out during ERCP. The method enables sampling through the majority of locations within the biliary and pancreatic duct pathways. Well-preserved cellular samples appropriate for cytological examination are typically present in well-prepared and collected specimens [12,13].

In the current investigation, cancer was prevalent in the older age group. Additionally, women were more often impacted than men. Other authors [14,15] made comparable conclusions. In spite of great test specific (90-100%), most investigations to far have found rather modest detection sensitivity (33-78%; mean 42%) and a negative predictive value. A comparison of the sensitivity, specificity, negative predictive value, and positive predictive value of several studies

The technique in the current investigation demonstrated a modest diagnostic sensitivity of 67.5%. A skilled gastrosurgeon carried out the procedure, and smears were evaluated in accordance with protocol. Most studies' low sensitivity may be the result of inconsistent sampling and interpretation. When cancers at these sites have a predominately submucosal distribution with little to no surface epithelial abnormalities, sampling mistakes may happen [16,17]. External compression, such as that brought on by lymph node metastases, might also result in restrictions. The sensitivity may also be impacted by the tumor's location. In clearly distinct carcinomas, where the cytological abnormalities may be modest, interpreting errors are more likely to happen [18].

Diagnostic precision is highest for ampullary neoplasms, intermediate for cholangiocarcinoma, and lowest for pancreatic carcinoma, especially for tumours in the pancreatic tail, according to several investigations [19]. Although in this study, the detection rate for ampullary carcinoma cases was 80%,

cholangiocarcinoma cases were 87.5%, pancreatic ductal adenocarcinoma cases were 100%, and gall bladder-obstructing carcinoma cases were 56%.

The fact that the detection rate increased throughout the second half of the research was an intriguing discovery from the current investigation. Possible explanations include the use of double lumen brushes later in the trial in place of single lumen brushes and an improvement in the surgeon's skill level when taking the sample. In order to raise the cellular production, the brush was also moved more front. Additionally, in comparison with extracting the brush through the catheter sheath, discarding the brush and capillary simultaneously enhanced cancer detection.

According to the current study, cytological characteristics such as high cellularity, loss of polarity, hyperchromatic nuclei with clumped chromatin, nuclear crowding, uneven nuclear membrane, and nucleolar prominence were shown to be more consistent with malignancy. In smears that were reported as positive, nuclear variability, background atypical cells, and multinucleate cells were also observed.

Inflammation-related cytological characteristics were common in both benign as well as malignant bile duct brushings, making it difficult to distinguish between the two. However, it should be highlighted that severe swelling shouldn't always be disregarded, especially if it's joined by other alarming signs of cancer. Five of our cancer smears revealed ambient inflammation, and only a handful of the clusters were abnormal. Many researchers have come up with distinct diagnostic standards for carcinoma in an effort to increase the diagnostic precision of cytologic testing.

Seven assessors looked at the effectiveness of numerous widely recognised cytological characteristics to predict cancer in bile duct brushing samples by Avadhani V et al. [20]. They discovered that chromatin pattern changes, nuclear irregularities, pleomorphism, 2-cell populations, and three-dimensional groups, which were seen in more than 50% of cases, were useful in precisely detecting cancer in these samples. Strict morphologic elements were explored by Okonkwo AM et al., including main criteria (nuclear shape, chromatin arrangement) and minor factors (polarity, cell kinds, nuclear size, nuclear grooves, nucleoli, mitosis, nuclear/cytoplasmic ratio). The most consistently helpful characteristics that were associated with cancer were aberrant chromatin arrangement and abnormalities in nuclear membrane, which are similar to the criteria we have researched. Their study, like this study, was founded on conventional smears [21].

The overall assessment of malignancy based on the degree of atypia, on the other hand, was shown to be more reproducible than any other set of criteria, and it also produced increased sensitivity for malignancy with just a slight drop in specificity [22]. It has been shown that pancreatic ductal adenocarcinomas, in particular its micropapillary and indistinguishable variants, may demonstrate marked intra-epithelial penetration in pancreatic ductal adenocarcinoma, which can involve the bile ducts and lead to "positive" bile duct brushings [23].

In order to make a definitive diagnosis of cancer, the oncologist should perform repeated sample if there are no clear characteristics of carcinoma. In our analysis, two individuals got multiple aspirations since there was a high clinical and radiological suspicion of cancer in both of them. There were no procedure-related problems in the current study. One retroperitoneal bile duct perforation associated with brushing was described by Ponchon T et al. in a series of 223 consecutive biliary strictures collected by brush cytology. The patient underwent biliary stent installation as treatment and showed no symptoms after that. These brushings weren't done with a guide wire; this adverse event is less likely to occur when brushing is done over a guide wire [24].

In light of new research on adjuvant studies for bile duct brushing testing, immunohistochemistry is a further valuable diagnostic tool for brush cytology. Over 50% of biliary tumours in a recent study displayed a maspin +/IMP3+/S100P+/pVHL staining profile, while 20% displayed a maspin +/IMP3 /S100P+/pVHL profile [25]. Immunohistochemistry, however, lacks sensitivity. With a sensitivity of 65% and specificity of 93%, a more recent generation of pancreato-biliary tract-specific FISH probes has been found that targets 1q21, 7p12, 8q24, and 9p21 [26]. FISH, however, faces both technological and budgetary difficulties.

In an effort to increase the diagnostic precision of bile duct brushings, some have proposed triple testing (brush cytology, fluorescence in situ hybridization, and forceps biopsy), which has higher sensitivity, specificity, positive predictive value, and negative predictive value than brushing alone (82%, 100%, 100%, and 87%, respectively) [27]. In contrast to clinical practise, which frequently lacks sufficient specimen cellularity for subsequent testing, most centres lack the necessary capabilities, and molecular assays are not cost-effective, the samples used in these investigations did.

CONCLUSION:

To sum up, the findings of the present study clearly demonstrate that biliary brushing is beneficial and economical if the following recommendations are adhered to: 1) Smears are properly created using a double lumen brush during sample collection, moving more forward than backward; 2) stringent cytological criteria are followed for interpretation and reporting. Brush cytology is effective as the initial inquiry of patients with suspected pancreatico-biliary neoplasia, and the current study satisfies the need to examine individual morphological traits and demonstrate their diagnostic value. However, the technique's limits must be acknowledged.

Future recommendations include the creation of methods for better lesion targeting and the retrieval of cytology specimens of higher quality. Studies with more cases, as well as multi-reviewer analysis, also add to the computation of the procedure's diagnosing efficacy.

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