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Cytodiagnosis of cutaneous metastasis from colonic adenocarcinoma in a young male -Report of a case with Literature Review

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Abstract
Metastasis can occur at any age but the incidence rises with advancing age, especially after fifth decade of life and is uncommon in young patients. Cutaneous metastases are of diagnostic importance because they may be the first manifestation of an undiscovered underlying malignancy or first indication of recurrence of a treated malignancy. Fine needle aspiration cytology (FNAC) is a simple minimally invasive rapid method for diagnosis of cutaneous metastasis in patients without any complication. It allows an immediate initial evaluation of the patient to plan an effective course of treatment. We discuss a 21 year-old patient with ascending colon adenocarcinoma who subsequently developed cutaneous metastases emphasising the role of FNAC over biopsy in diagnosing metastatic skin nodules and evaluation of cutaneous nodules.

Keywords: Cutaneous, Nodules, Metastases, Colon adenocarcinoma, Cytology, Skin metastases, FNAC.

Introduction
Cutaneous metastases of colorectal carcinoma in young patient are quite rare. Colorectal carcinoma has been a disease of older age group with more than 90% of colorectal cancer occurring in patients above 55 years of age and rarely presents in adolescence and young individuals, below 25 years of age. When presenting in younger individuals well known predisposing factors are usually present such as inflammatory bowel disease, familial adenomatosis polyposis, and hereditary nonpolyposis colon cancer (HNPCC).[1,2,3]

Though presenting features of the tumor show only subtle differences in clinical presentation in the two age groups but this tumor less often finds place in differential diagnosis of mucinous tumors in younger age group, especially cutaneous nodule despite carrying significant clinical implications .We report here a case of 21 year old young male presenting with cutaneous metastases of mucinous colorectal carcinoma on cytology discussing various cytological features of mucinous adenocarcinoma, important differential diagnoses of cutaneous metastatic nodule in young patients and emphasizing the importance of fine needle aspiration cytology in such patients over biopsy. In cases where cutaneous nodule is a primary presentation of malignancy FNAC permits early and prompt, initial diagnostic evaluation of patient and in patients with known internal malignancy, FNAC being inexpensive and less cumbersome procedure confirms the clinical diagnosis of metastatic nodule with high sensitivity and specificity with minimal chances of tumor seeding. Biopsy of such lesions offer no added advantage.[3,4]

Case Report
A 21-year old patient came to the department with multiple cutaneous nodules over lower abdomen near an abdominal surgical scar mark. The nodules were hard, fixed and painless with size varying from 1cm to 4.5 cm in diameter. FNAC of the cutaneous nodules was performed and thick mucoid material was aspirated. Smears prepared were stained with Giemsa stain and papanicolaou stain. Cytology smears showed few small clusters and sheets of atypical cells with moderate amount of cytoplasm in a background of abundant mucin. A provisional diagnosis of metastatic mucinous carcinoma was made and on taking detailed history following details were revealed. The patient was admitted one year back with chief complaints of pain in abdomen and inability to pass stools for three days. He was admitted, investigated and diagnosed as a case of intestinal obstruction. Computed tomography (CT) scan showed an ill defined heterogeneous enhancing mass lesion involving ascending colon extending from ileocecal junction to hepatic flexure. Right hemicolectomy and excision of tumor was done. Histological examination of the mass revealed mucinous adenocarcinoma with nodal metastases (three out of ten lymph nodes). And lymphovascular invasion. Postoperative chemotherapy was. Magnetic Resonance Imaging also showed metastatic lesion on abdominal wall along with hepatic metastasis, bilateral moderate hydroureteronephrosis and chronic granulomatous lesion in spleen. Palliative treatment with radiotherapy was initiated and patient is under follow up.

Discussion and Review of Literature
Cutaneous metastases derived from internal visceral malignancies are rare and the reported incidence ranges from 1.4% to 10% of all visceral

cancers.[5] The general incidence of cutaneous metastasis of gastrointestinal neoplasms is about 5.3% and frequency of skin metastasis of colorectal carcinoma has been reported to be 2.3-6%. Incidence of tumors metastasizing to the skin correlates well with the frequency of occurrence of primary malignant tumours in each gender.[6,7] In males there is higher incidence of cutaneous metastases, from lung cancer (20%–30%) followed by colorectal (16.3%), esophageal carcinoma, renal cell carcinoma, melanoma and carcinoma of the oral cavity. while in females the most common tumors are breast cancer (70%), followed by colorectal (1.5%), ovarian cancer, lung cancers, melanoma and sarcoma.[7,8] The common sites of cutaneous metastasis include chest wall, anterior abdominal wall, lower extremities, neck, back, upper extremities, face and pelvis.[9] Localisation site of metastases may provide a clue towards underling malignancy as most of the tumors spreads to skin near primary malignancy .Chest nodules are more common in patients with lung and breast carcinoma while lower back involvement is seen in renal cell carcinoma. Periumblical nodules, also known as Sister Mary Joseph nodule are common in gastrointestinal malignancies i.e stomach and colorectal carcinoma.[10]

The most frequent sites of cutaneous metastates from colorectal carcinoma is abdomen, especially on the postoperative surgical incision scars, seen in upto 0.6%-3% of all patients. This may not be exclusively on the surgical incision scar for the tumor excision but even on any preexisting unrelated operative scars. Other cutaneous sites in order of decreasing frequency are the pelvis, back, chest, upper extremities, head and neck. Rare reported sites of skin metastasis of colorectal cancer include scalp, face, eyelids, tip of the nose, nostril, forearm, perineal region, ankle and big toe.[5,6,11,12] Extensive literature search was done using keywords-cutaneous metastases, colorectal carcinoma, gastrointestinal adenocarcinoma, skin metastases and the cases reported in the last ten years and cases were studied and tabulated.(Table 1)

Table 1: Cutaneous metastases of Colonic adenocarcinoma in previous ten years

Site Of Metastasis	Age/Sex (Years)	Primary Tumor Site	Time Of Previous Surgery	Year	Reported By
Abdomen	21/M	Ascending colon		2017	Present case
Chin	69/M	Colon	3 Years	2006	Fyrmpas G et al[17]
Scrotum	72 /M	Colon	8 months	2009	McWeeney DM et al[18]
Heart	70/F	Sigmoid colon	simultaneous	2009	Choi PW et a l[19]
Upper Lip	65 /M	Rectum	3.5 Year	2010	Saladzinskas Z et al[20]
Abdomen (Hysterectomy scar)	72/F	Sigmoid colon	simultaneous	2010	Gupta SS et al[21]
Larynx	NA	Rectum	NA	2011	Ta JQ et al[22]
Scalp	53 /M	Sigmoid Colon	2.5 Years	2011	Horiuchi A et al[23]
Left Paravertebral	72 /F	Colon-rectum	3 Years	2012	Russo GL et al[24]
Left Buttock	78 /F	Right Colon a	8 Months	2012	Gomes CMCN et al[25]
Lower Extremities	36 /M	Ascending Colon	>2 Yrs	2012	Rajan D et al[26]
Periumblical/ Lower Abdomen	80 / M	Colon	1 yr	2013	Nesseris I et al[27]
Face	70 /M	Rectum	4 yrs	2013	Hashimi Y et al[28]
Scalp	62/M	Colon	4 Months	2015	Fragulidis G et al[29]
End Ileostomy Site	64/M	Sigmoid Colon	7 Yrs	2015	Ozgur I et al[30]
Perineum	40/F	Rectum	1 month	2015	Varma K et al[31]
Genital Area, Bilateral Groin, Perineum	47 /M	Rectum	1 Yr	2016	Dehal A et al[32]
Abdomen (3 cases)	31 – 76 Exact age NA	Colon	NA	2016	Sharma A et al [33]
Scalp	76/M	Descending colon	simultaneous	2016	Góes HF et al[34]
Scrotal	NA			2016	Udkoff J et al[35]
NA-Not available					

Most of these cases were diagnosed on histology and cases of mucinous adenocarcinoma of colon with cutaneous metastases in cytology still remain a rare entity. Clinically these cutaneous metastases can manifest as non inflammatory nodules (more common) or inflammatory nodules, sometimes even with erythrema and ulceration or even as more diffuse cellulitis-like lesions. They show variable features, from being violaceous, flesh-colored to pale nodules, can be solitary or multiple but are usually firm, freely mobile, painless nodules.[13] Clinical mimics include epidermal cysts, neurofibromas, lipomas, cicatricial morphea-like plaques, lymphoma and alopecia.(Table 2)[31-33]

Table 2: Differential Diagnosis of Cutaneous Nodule

Inflammatory /Nonneoplastic	**Metastatic tumors**
Abscess Haematoma Necrotizing fascitis Cutaneous cysticercosis Epidermoid cyst Endometriosis Foreign body granuloma Abdominal wall vascular malformation	Metastatic Adenocarcinoma - Breast ,Stomach, , Lung.,gall bladder ,Colorectal carcinoma Metastatic Squamous cell carcinoma –Lung,esophagus Metastatic melanoma Small cell neurendocrine carcinoma of salivary gland Neuroendocrine carcinoma of visceral organ Renal cell carcinoma Cholangiocarcinoma Hepatocellular carcinoma Thyroid - Hurthle cell carcinoma Transitional cell carcinoma Prostate adenocarcinoma Non- Hodgkin Lymphoma -Anaplastic Large Cell Lymphoma Diffuse large B cell lymphoma Sarcoma – Rhabdomyosarcoma, Epitheloid sarcoma, Leiomyosarcoma, Malignant fibrous histiocytoma Ewing's sarcoma Chondrosarcoma Multiple Myeloma
Neoplastic	
Primary tumors Skin – Squamous cell carcinoma, Basal cell carcinoma, Malignant Melanoma,Merkel cell carcinoma Primary adnexal tumors Soft tissue tumors – Lipoma,Neurofibroma,Hemangioma Desmoids tumor,Dermatofibroma, Dermatofibrosarcoma protuberans,Subcutaneous leiomyoma	

Early recognition of tumour relapse from a suspicious skin lesion may lead to initiation of treatment before widespread metastases occur. As an alternative to performing biopsies, fine needle aspiration cytology (FNAC) is a minimally invasive method that can be used to diagnose these cases. It is a relatively simple, rapid and inexpensive procedure with high sensitivity and specificity in evaluating these cases. Avoiding unnecessary surgical intervention Most reported cases of cytodiagnosis of mucinous nodules describe tumors with atypical cells lying in a necrotic background.[34,35] In present case small cell clusters and sheets of atypical cells were seen embedded in a background of large amount of extracellular mucin. (Fig (Fig). 1(a) (b)) Cytological aspirate from predominantly mucinous areas of the tumor show cells with mild nuclear atypia and moderate amoumt of basophilic cytoplasm. embedded in mucin as compared to other areas showing markedly pleomorphic cells lying in a necrotic background. (Fig. 2(a) (b))Presence of pools of extracellular mucin, signet cells and three dimensional papillae represent metastases rather than primary in case of adenocarcinoma.

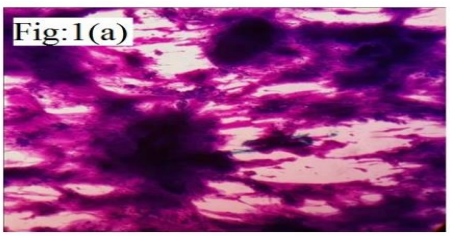

Fig. 1(a): FNAC smears showing few clusters of atypical cells in a background of abundant magenta-colored mucin (Giemsa stain, 40X)

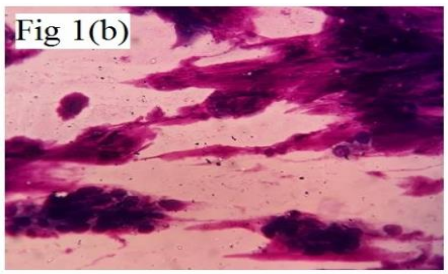

Fig. 1(b): Higher power view showing clusters of atypical cells (Giemsa stain, 400X)

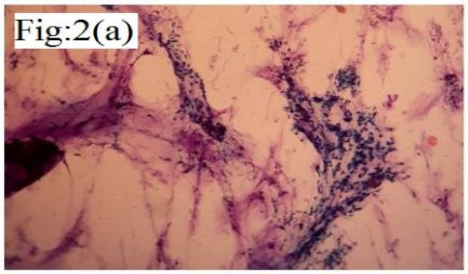

Fig. 2(a): FNAC showing few clusters of atypical cells in a background of abundant mucin (Papanicolaou stain, 40X)

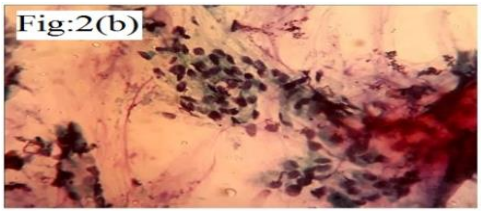

Fig. 2(b): Higher power view showing clusters of atypical cells in a background of mucin (Papanicolaou stain, 400X)

Pathologically these metastases usually have a nodular configuration and are located in the deep dermis, with subsequent spread to the epidermis and subcutaneous tissue. (Fig. 3)Overlying skin is usually free from tumor.[4,13,36,37] Histologically, these can be adenocarcinoma, squamous cell carcinoma, undifferentiated carcinoma and other miscellaneous types. Adenocarcinoma from various organs was the commonest to metastasize, similar to a study by Bansal et al.[7,37] These metastatic lesions need to be distinguished from primary adnexal tumours and primary squamous cell carcinoma of the skin. Most skin metastases from large intestine tumors are well differentiated, often mucin-secreting adenocarcinomas. (Table 3)

Fig. 3: Cutaneous metastatic nodules from colonic adenocarcinoma on anterior abdomen

Table 3: Differential diagnosis of cutaneous mucinous tumors

Ovarian mucinous carcinomas
Gastric mucinous carcinoma
Signet ring cell carcinoma stomach
Intestinal/Appendiceal mucinous carcinoma
Pancreatic Mucinous cystic tumor-
Mucinous type of cholangiocarcinoma
Mucinous carcinoma of gall bladder
Intraductal papillary mucinous tumor of bile duct and pancreas
Pseudomyxoma peritonei
Mucinous adenocystic carcinoma of the skin

Mucinous adenocarcinoma comprises about 10% to 15% of all colorectal carcinomas. In the World Health Organization (WHO) classification, mucinous adenocarcinoma (MA) is defined as an adenocarcinoma in which >50% of the lesion is composed of pools of extracellular mucin. Tumor with <50% of the lesion composed of mucin is categorized as having mucinous component. This variant is characterized by pools of extracellular mucin that contain malignant epithelium as acinar structures, strips of cells or single cells.[38] However, an average of 28% of the lesions found in younger patients constituted mucinous tumors compared with an average of 5% for adults with colorectal carcinoma. Presence of pools of extracellular mucin, signet cells and three dimensional papillae represent metastases rather than primary in case of adenocarcinoma. (Fig. 4(a) (b) (c))

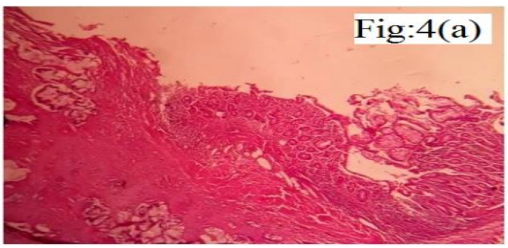

Fig. 4(a): Histopathology showing colonic mucosa with few typical cells floating in pools of extracellular mucin (Haematoxylin and Eosin stain,40X)

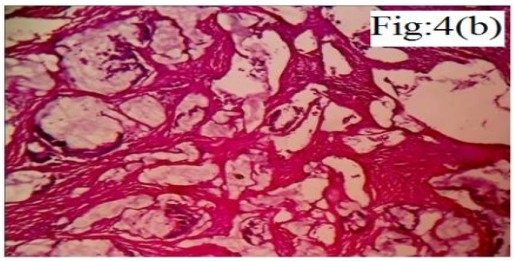

Fig. 4(b): Histopathology of primary colonic adenocarcinoma showing atypical cells floating in pools of abundant abundant extracellular mucin (Haematoxylin and Eosin stain 100X)

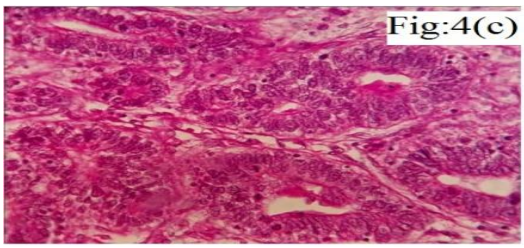

Fig. 4(c): Histopathology of primary colonic adenocarcinoma showing atypical glands with loss of mucin, nuclear stratification, nuclear atypia and mitoses (Haematoxylin and Eosin stain 400X)

Cutaneous metastasis can be due to contiguous (direct) or non contiguous (distant) spread. The non contiguous spread is through lymphogenous spread or intravascular dissemination. Besides these, direct extension of tumor and surgical implantation can occur . Wong et al added the tumor spread can also along occur along embryonal remnants such as the urachus.[24,39]

Colorectal carcinoma is believed to metastasize initially through lymphatics and later through the haematogenous route.It metastasize by the bloodstream to remote organs of the body, such as the head and extremities. Bloodstream skin metastases are characterized by the absence of regional lymph node involvement, then development of extensive skin metastases, venous invasion of tumor cells within skin metastases, and the presence of tumor cells in the pulmonary bloodvessels. Sometimes, primary sites have not been located even after autopsies [24,40,41]

On the average, skin metastases occur after two years to 4.9 years following the excision of the primary tumor. Cutaneous metastases typically signify widespread disease occurring due to systemic spread and thus, represent terminal stage of malignant disease with poor prognosis.[7,17,31,42]

Conclusion

Though metastatic cutaneous metastases in young men is rare but there should be be a broad differential diagnoses to be considered and FNAC is an important initial investigation which is reliable and accurate in diagnosis of such cutaneous nodules.

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Conflicts of Interest: None
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