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Dermatological Manifestations of Gastrointestinal Tract Malignancies: A Rare Prospective Study

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ABSTRACT
Background: *Dermatological manifestations of gastrointestinal tract (GIT) malignancies can be specific like cutaneous metastasis and nonspecific like paraneoplatic disorders and genodermatosis. They are protean but uncommon and usually appear during advanced stage of underlying malignancy. Sometimes they are presenting sign of an occult malignancy or represent recurrence of malignant process at first. The detection of this presentation is of utmost important for both clinician and patient.*
Objective: *To determine the frequency of dermatological manifestations of GIT malignancies.*
Material and Methods: *140 patients of proven GIT malignancies were enrolled over a period of one year. Detailed history was taken, further head to toe examination of skin, hair, nails and mucosae were done. Procedures like skin biopsy, KOH examination, tzanck smear examination and imaging investigations were performed as per need to confirm our clinical diagnosis.*
Results: *Out of 140 patients, 5(3.6%) patients developed rare paraneoplastic manifestations in the form of Bazex syndrome, PPP (Pancreatitis panniculitis polyarthritis) syndrome and acquired palmoplantar keratoderma. 3(2.1%) patients had metastasis to skin. One (0.7%) patient of Neurofibromatosis had adenocarcinoma of stomach. Other non-specific mucocutaneous manifestations were found in 71(50.7%) patients.*
Conclusion: *It is emphasized that metastasis, genodermatosis and paraneoplastic dermatosis are very rare but detectable cutaneous manifestations of GIT malignancies. They may act as first sign to diagnose an asymptomatic underlying malignancy. Through high clinical suspicion and active diagnostic workup, a dermatologist/clinician can improve the patient's prognosis by early detection and timely referral for treatment in such cases.*
Keywords: *skin manifestations, GIT malignancies, metastasis, paraneoplastic syndromes.*

INTRODUCTION

Skin manifestations of GIT malignancies are quite infrequent, further there is scarcity of prospective studies depicting these manifestations. GIT malignancies involve skin by three types of disorders including cutaneous metastasis, paraneoplastic syndromes and genodermatosis (familial cancer syndromes). In 1868, Hebra was the first to describe the skin pigmentations as an indicator of underlying visceral malignancy. Since that time more than 50 paraneoplastic disorders have been reported as potential markers of malignancy.[1] Acanthosis nigricans maligna (ANM) is the first and perhaps the best well known condition initially reported by Pollitzer and Janovsky in 1890.[2] Bazex syndrome, Leser trelate sign, erythema gyretum repens, Plummer Vinson syndrome, necrolytic migratory erythema and carcinoid syndrome are other paraneoplastic dermatosis strongly associated with GIT malignancies.[3] According to Curth's postulates, paraneoplastic lesions do not contain malignant cells, malignancy and paraneoplastic disorders start simultaneously, then run a parallel course and statistically significant association exists between the paraneoplastic syndrome and underlying malignancy.[4]

Skin metastasis is seen in 0.7% to 10.4% of all patients with cancers. Metastasis from GIT malignancies to skin accounts for less than 5% of cases.[5] Skin metastases may be the first sign to represent an occult malignancy or to reflect a recurrent malignant disease. Further being the largest and most visible organ, skin metastasis is easy to detect earlier as compared to other organs. Skin metastasis usually signifies widespread terminal disease with a poor prognosis. It is a high clinical suspicion and active histopathological evaluation of biopsy specimens which can explore both skin disorder and underlying malignancy at early stage.

GIT and skin have closely linked developmental origin, so a number of genodermatosis affect GIT and skin simultaneously. Amongst them are hereditary cancer syndromes like nonpolyposis and polyposis colorectal cancer, hamartomatous polyposis, and Cronkhite Canada syndrome. These syndromes are genetically acquired and caused by mutations in tumor suppressor genes. Familial cancer syndromes have prominent cutaneous features; their appropriate diagnosis can direct a clinician to suspect and screen for predisposed underlying malignancy.[6]

MATERIAL AND METHODS

Study design: This is an observational study performed over a period of one year starting from August 2013 to July 2014. All histopathologically proven cases of GIT cancers (who were admitted in surgery ward and had registration in the department of Radiotherapy and oncology) were included. Those patients who were on radiotherapy, chemotherapy or with severe systemic illness or on drugs known to produce dermatosis mimicking paraneoplastic syndromes were excluded from this study. Only cases of primary GIT malignancies were taken. Those cases were excluded in which involvement of GIT was secondarily due to metastasis from distant organs or due to invasion from adjacent organs (e.g. kidneys, ovaries, lungs etc)

Methods

An informed consent was signed by every patient. A detailed dermatological work up including history, examination and relevant investigations was performed. A clear history about the duration between the diagnosis of malignancy and onset of skin lesions was taken. Demographic profile, personal and family history was also taken. Details of site and histopathological type of underlying GIT cancer were noted down from the treatment file of the patients. General physical examination and mucocutaneous examination was done on every patient in natural light. Hand held lens was used for the examination of skin lesions and white torch light for mucosal examination. All findings were noted on proforma specially designed for this study. Clinical diagnosis was supplemented by laboratory, imaging and

cytological/histopathological procedures wherever required. KOH examination for fungal infections, tzanck smears for viral infection, skin biopsy for confirmation of metastatic lesions was performed. Further laboratory, radiological investigations and immunofluorescence studies were also advised for those patients who directly presented with skin lesions and later on proved to have underlying GIT malignancy.

RESULTS

Out of total 140 patients, 80(57.14%) patients had mucocutaneous manifestations. 5(3.6%) patients had paraneoplastic dermatosis and 3(2.1%) had metastasis to skin. One (0.7%) patient of neurofibromatosis developed adenocarcinoma of stomach. 71(50.1%) patients had non-specific skin, hair and nail changes.

The most common age group affected was fourth through eighth decade of life. 61.4% were males and 38.6% were females with male to female ratio of 1.6:1. This indicates that GIT malignancies are more common in males of elderly age group. Family history was positive only in a single case of Neurofibromatosis.

On general physical examination, pallor was the most common finding present in 48(34.3%) cases. Amongst the primary tumors, stomach was the most commonly affected organ in 47(33.6%) cases followed by colon in 25(17.9%) cases and then rectum in 23(16.4%) cases. Further on histopathology, adenocarcinoma was most common type followed by squamous cell carcinoma and signet ring cell types. Adenocarcinoma predominantly originated from stomach and colon while squamous cell carcinoma had origin primarily from esophagus and rectum.

In our study out of total 140 patients, 25 (17.8%) patients had metastasis to multiple internal organs like liver, lung, peritoneum and lymph nodes, while skin metastasis was observed only in 3(2.1%) cases. This finding suggests that skin is comparatively a rare site for metastasis. Out of these three cases, one patient had adenocarcinoma gall bladder which presented with Sister Mary Joseph nodule (Figure1&2). Second case had adenocarcinoma stomach in terminal stage and presented with three metastatic nodules over abdomen, while third case had carcinoma of esophagus with metastatic nodule over neck. Thus nodular lesion metastasizing to abdominal wall was found as more common presentation. As per relation between onset of skin lesions and diagnosis of underlying malignancy, two patients had concurrent onset while one patient developed metastasis to skin five months after diagnosis of primary tumor. All three cases had non-contiguous mode of spread.

Amongst paraneoplastic dermatosis, Bazex syndrome (Figure 3&4) was found in 2 (1.45%) patients and it was associated with adenocarcinoma of stomach and colon. One patient had concurrent onset of skin and GIT symptoms while other patient developed skin lesions seven months prior to the diagnosis of underlying tumor. A very rare case of PPP syndrome with triad of panniculitis, polyarthritis and pancreatitis was encountered. Patient presented with multiple erythematous, tender skin nodules (Figure 5) [HPE proven panniculitis (Figure6)] along with symptoms of acute pancreatitis. Later on he developed arthritis of multiple joints (Figure 7). On HRCT of abdomen a malignant mass was appreciated in pancreatic region (Figure 8) which was confirmed as adenocarcinoma of head of pancreas on excisional biopsy performed during exploratory laprotomy. Two (1.4%) cases of paraneoplastic palmoplantar keratoderma were observed. The onset of skin lesion was concurrent with the diagnosis of underlying adenocarcinoma of stomach and esophagus. A single (0.7%) patient of neuro-cutaneous syndrome was observed. He had neurofibromatosis type 1 (NF-1 diagnosed at age of 12 years) and developed adenocarcinoma of stomach at the age of 28 years.

Non-specific manifestations were recorded in 71(50.7%) patients in the form of xerosis being the most common finding in 17(12%) patients followed by pruritus in 6(4.3%) and multiple

seborrheic keratosis in 6(4.3%) patients. Other manifestations were non-praraneoplatic acanthosis nigricans (3.5%), non-paraneoplastic palmoplantar hyperkeratosis (2.1%) and skin infections (3.6%). Amongst skin appendages, nail manifestations were present in 27(19%) patients in the form of clubbing, onychomycosis, koilonychias and beau's lines etc. On mucosal examination oral candidiasis was present in 8(5.71%) cases and atrophic glossitis in 7(5%) cases. Two (1.4%) cases of diffuse hair loss were also found.

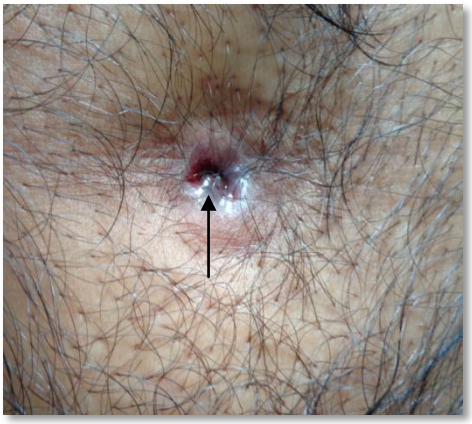


Figure 1: Sister Mary Joseph nodule in a adenocarcinoma of gall bladder

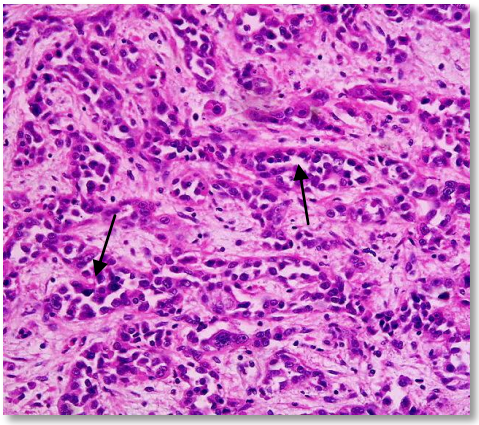
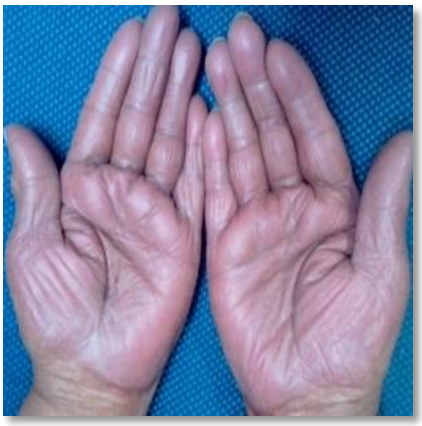


Figure 2: Metastatic deposits of adenocarcinoma patient of gall bladder showing ill formed glands by neoplastic cells.



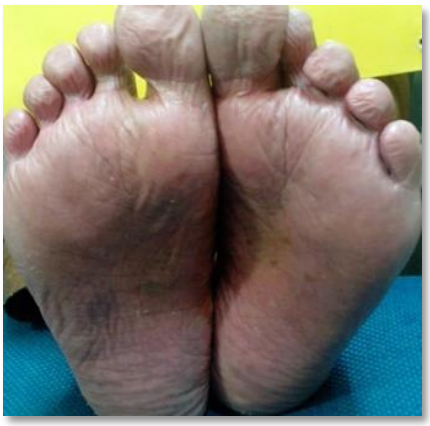


Figure 3,4: Bazex syndrome showing violaceous, psoriasiform palmoplantar keratoderma.

PPP Syndrome in a patient of carcinoma head of pancreas

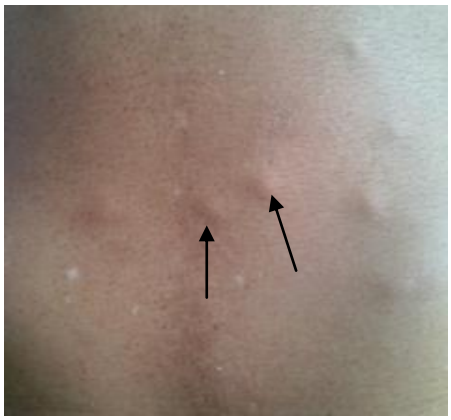


Figure 5: Multiple nodules of Pancreatic Panniculitis.

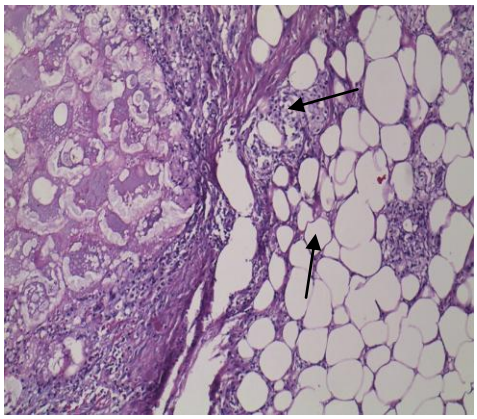


Figure 6: Septal and lobular panniculitis with Ghost-like anucleated cells on HPE

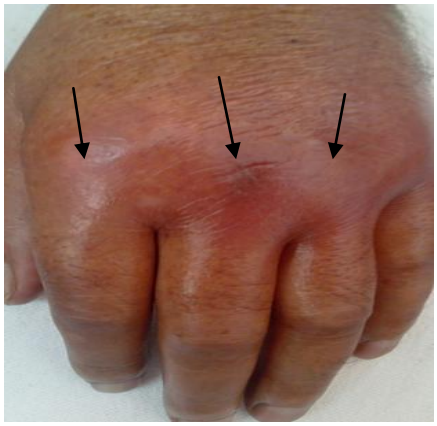


Figure 7: Polyarthritis of metacarpophalangeal joints.

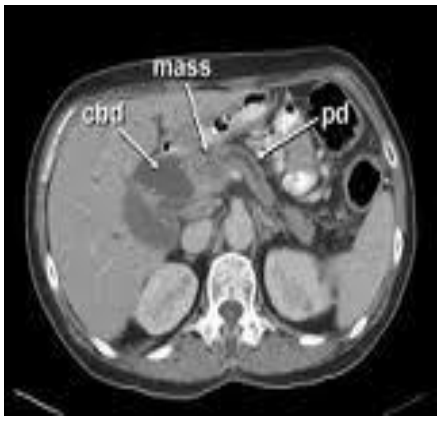


Figure 8: Mass in head of pancreas on CT scan.

DISCUSSION

Numerous skin disorders have been described in association with malignancies of GIT. In some cases skin is infiltrated directly or indirectly by cancer cells that represent cutaneous metastasis. In other cases, the skin lesions are produced due to various factors released during tumor growth, but they do not contain malignant cells, they are referred as paraneoplastic syndromes. Thirdly there are some genetically inherited syndromes which affect both skin and GIT, further they carry a high risk for development of GIT malignancies. Here we discuss all three components along with other non-specific cutaneous manifestations of GIT malignancies.

The incidence of cutaneous metastasis from visceral malignancies is 5.3% and range is 0.7% to 9%.[5] Hu SC et al evaluated 12,146 patients of internal malignancy and found cutaneous metastasis in 124(1.02%) cases [7] while Omranipour et al reported skin metastasis in a range of 0.7-10.4% of all cancer patients. [5] Our results are consistent with above studies depicting that skin is a less common site for metastasis. The incidence of cutaneous metastases from carcinomas of the upper digestive tract has been reported as less than 1%. [8] SCC of esophagus rarely shows any metastasis to skin. In a study of 7316 cancer patients with cutaneous metastases, no patient with esophageal carcinoma was observed [8] and in a study of 4020 cancer patients by the same authors, only 3 cutaneous metastases were of the esophageal origin.[9] The reported cutaneous metastasis originated from esophageal adenocarcinoma rather than SCC.[10] In our study all three cases of cutaneous metastasis had underlying carcinoma of upper GIT (esophagus, stomach and gall bladder). This predisposition is related to prone life style and dietary habits of our population for upper GIT cancers. [11] Gastric carcinoma most commonly metastasizes to umbilical region and often referred as the Sister Mary Joseph nodule. Its incidence is 1%–3% of all intra-abdominal and pelvic malignancies. Among all reported cases of Sister Mary Joseph nodule, 35%–65% metastasize from GIT malignancies (stomach, rectum, pancreas and gall bladder). [12] We found this presentation in a case of carcinoma gall bladder. Colorectal adenocarcinoma usually metastasizes to incisional scars over perineum and abdomen. In a study of 413 patients with metastatic colon cancer, out of 18 patients (4.4%) with skin metastases, eleven patients had scar metastasis to abdominal incisions. [13] Scar metastasis may be the first sign to represent underlying malignancies of colon, rectum, liver and oral cavity. [13] Our observation was according to literature describing that adenocarcinoma is more prone for metastasis than squamous cell carcinoma and nodule is the most common clinical morphology. Zosteriform or erysipelas- like pattern, simple papule, plaque and non-healing ulcer are other reported presentations of skin metastasis. [14] Non-contiguous mode was

predominant type of spread in our study. This finding corresponds with literature reports showing non-contiguous mode of spread more common than contiguous. [15] We noted a mean interval of five months between the diagnosis of primary tumor and development of skin metastasis. A wide range from some weeks to more than a decade (longest being 13 years) has been reported by Kovacs et al. [16]

Bazex syndrome (a rare entity) is characterized by symmetrical psoriasiform eruptions over acral sites (ears, nose, cheeks, hands, feet, and knees). Later on lesions spread proximally along with development of palmoplanter keratoderma and nail dystrophy. Bazex syndrome is commonly seen with squamous cell carcinoma (SCC) of the upper aerodigestive tract. [6] We found Bazex syndrome in two patients with primary tumor of stomach and colon, this association has also been reported in the literature. [17-18] Skin lesions of Bazex usually precede the diagnosis of primary tumor in 65-70%, follow the diagnosis in 10-15% and have concurrent onset in 15-25% of cases. [19] In our study one (50%) patient developed skin lesions seven months prior to the diagnosis of adenocarcinoma stomach, while another patient (50%) had concurrent onset.

The triad of pancreatitis, panniculitis and poly-arthritis is known as PPP syndrome. It is a very rare condition with only 25 cases reported in literature so far. [20] Skin lesions are presenting features in about 40% of pancreatic panniculitis. Panniculitis is present in only 2% patients of pancreatic disorders, while in 80-100% cases of pancreatic panniculitis, the underlying condition is either pancreatitis or pancreatic carcinoma. [21] Ghost like anucleated cells with shadowy walls is pathognomic finding of panniculitis on histopat-hology. [20] Appearance of panniculitis can help in early diagnosis and treatment but PPP syndrome is associated with high morbidity and mortality.

Neurofibromatosis type 1 (NF-1) or von Recklinghausen's disease, is an autosomal dominant disorder with classical presentation by café-au-lat macules and multiple neurofibromas. Malignancies are found in 3% to 15% of patients. They usually have neurogenic or neuroendocrine (e.g.meningiomas, gliomas and pheochromo-cytoma) origin. [22] In GIT, gastrointestinal stromal tumours (GISTs) are seen frequently with NF1 but case reports of adenocarcinoma stomach and NF-1 are scattered. We found a case of adenocarcinoma of the stomach with NF-1 and same has been reported in the literature also. [23]

In our study the frequency of metastasis (2.14%), genodermatosis (0.7%) and classical paraneoplastic manifestations (3.6%) was found in accordance with the various studies described above. But after including non-specific manifestations of hair, nail and mucosae, overall prevalence of skin manifestations was found 57.14%. Although the range of overall cutaneous manifestations of internal malignancies is widely variable (4.26%-17.33%) in different studies [20, 24] but in comparison to these studies our results are much higher. The following factors may have role in this disparity; firstly non-specific hair, nail and mucosal changes have not been mentioned in above studies. Secondly post-operated hospitalized patients having various intubations, cannulations and parenteral nutrition were also the part of our sample. These factors predispose to poor hygiene, poor intake, immunosupression and various hospital acquired infections of skin and mucosae. Thirdly, GIT malignancies themselves predispose to nutritional deficit by poor intake, mal-absorption and excretory losses which further add up the number of non-specific manifestations. Lastly, the dry and cold weather of this area increased the number of cases with xerosis and pruritus.

CONCLUSION

From a practical prospective, all three components (metastasis, paraneoplastic syndromes and genodermatosis) of manifestations are quite uncommon and our study is the first series to describe these dermatological changes secondary to GIT malignancies. We emphasize that every suspected nodule must be biopsied and every

atypical dermatosis must be investigated in detail to detect underlying malignancy. Dermatologists may be the first physician to catch the terrible underlying tumor through these manifestations. Patient's prognosis can be improved by timely detection and early referral for treatment in such cases.

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