Revisiting cutaneous metastasis from carcinoma gall bladder

Sir,

Gall bladder carcinoma is the most aggressive tumor with poorest prognosis among all hepato-biliary cancers.[1] Gall bladder malignancy is common in north and central India with a strong female predilection.[2] Estimated female to male ratio of gall bladder carcinoma incidence in northern India is 10.1:1.01/100,000.[3] However, incidence is one-tenth in Southern India compared with north (0.0-0.7/100,000 women). Gall bladder malignancy in spite of being common in Indian subcontinent is still diagnosed at an advanced stage. The diagnosis evades common differentials especially when presenting in unusual ways. Skin is a site of both primary and metastatic malignancy. Metastasis to skin from internal malignancies is rare and portends a poor prognosis. Skin is commonly involved in metastasis from carcinoma breast, lung, colon and kidneys. Furthermore, skin metastasis from gall bladder is extremely uncommon with only few reports in the world literature. The common site for gall bladder to metastasize is the liver and draining lymph nodes.

A 76-year-old lady presented with 2-3 months history of multiple non-pruritic, painless subcutaneous

lesions on exposed areas of the face and upper trunk, not improving with routine measures prescribed by her personal physician. She had unquantified weight loss but no history of fever, night sweats or pruritus. Clinical examination revealed multiple 4-7 mm erythematous discrete papular lesions with no surrounding induration over her face, neck and trunk. There were no palpable nodes. There was mild fullness in the right hypochondrium. No mass was palpable.

She had normal hematocrit, mildly elevated aspartate transaminase (65.4 IU/L); alanine transaminase (133.6 IU/L) and alkaline phosphatase (211.8 IU/L). An excision biopsy from a skin lesion revealed subcutaneous tissue infiltration by neoplastic cells arranged singly. The cells were medium sized, with moderate cytoplasm and pleomorphic vesicular nuclei, some with prominent nucleoli. Numerous admixed lymphocytes, plasma cells and neutrophils were seen. Many apoptotic bodies were also noted [H and E, stain, Figure 1]. Features were of a poorly differentiated neoplasm. On immunohistochemical analysis, cells were positive for pan cytokeratin (CK), CK7 [Figure 2], focally for carcinoembryonic antigen (CEA) [Figure 3] and negative for leucocyte common antigen, thyroid transcription factor, CK20, CD30 and anaplastic lymphoma kinase. Ki 67 (mitotic index) was 50% in the large cells. Immunohistochemistry was suggestive of a metastatic adenocarcinoma possibly from the stomach, pancreatico-biliary tract or breast.

A computed tomography scan of the abdomen [Figure 4] revealed a minimally enhancing hypodense lesion in the gall bladder measuring 2.8 cm × 2.6 cm, infiltrating into segment IV of liver and subsegmental right hepatic ducts causing moderate intrahepatic biliary radical dilatation in both lobes. Multiple lymph nodes were seen in porta hepatis and along celiac axis causing mass effect. A hypodense lesion was

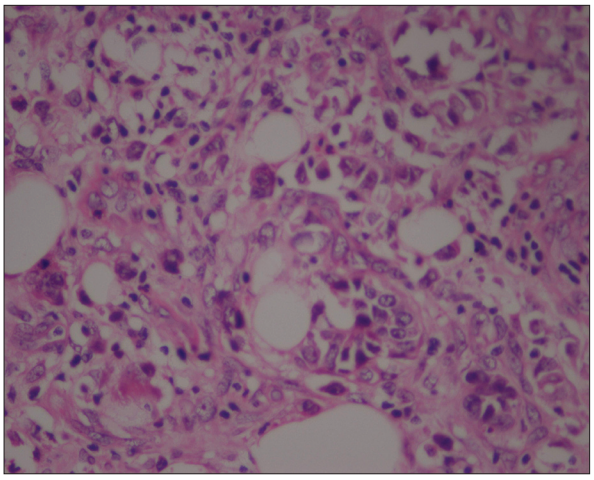

Figure 1: Subcutaneous nodules - H and E

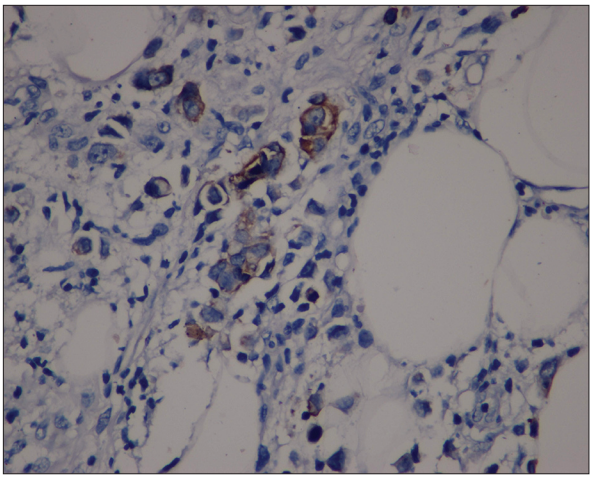

Figure 2: Subcutaneous nodules - cytokeratin 7

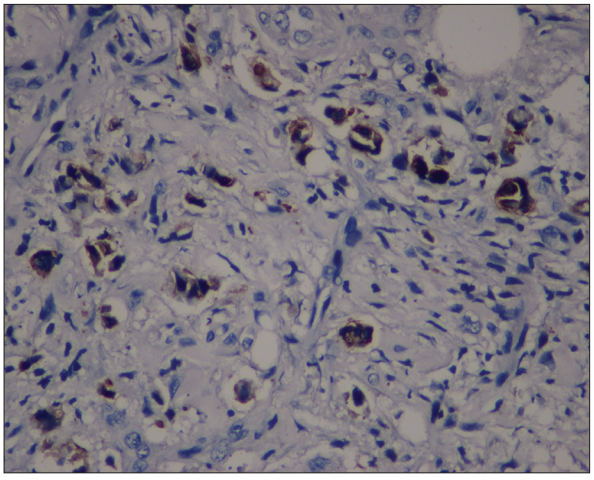

Figure 3: Subcutaneous nodules - carcinoembryonic antigen

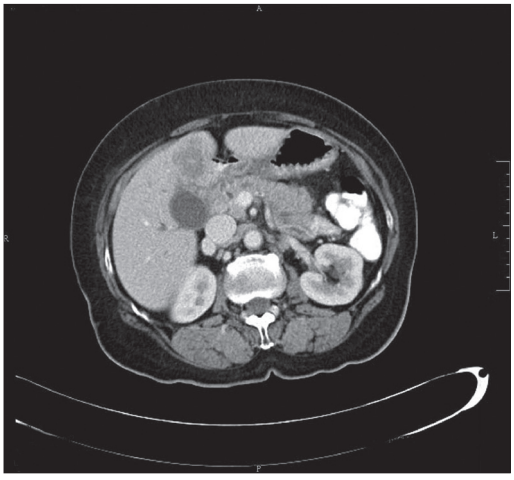

Figure 4: Computed tomography scan with gall bladder mass

seen in segment VII measuring 1.4 cm × 1.3 cm. An ultrasound guided biopsy from liver and gall bladder lesion revealed a poorly differentiated carcinoma with the same immunohistochemical pattern as the cutaneous neoplasm.

Her CA 19-9 was 50251 U/ml, serum CEA 12.55 ng/ml and alpha fetoprotein 47.11 ng/ml. She was administered palliative chemotherapy (gemcitabine/carboplatin), which produced complete resolution of skin lesions and 70% reduction in target lesion (Response Evaluation Criteria in Solid Tumors criteria). Her CA 19-9 dropped to 2765.8 U/ml. Post fifth cycle of treatment she had severe fatigue and further treatment was discontinued. A few weeks later her CA 19-9 began to rise and her general condition deteriorated rapidly. She succumbed to her illness 3 months later (7.5 months from the day of diagnosis).

In a large retrospective analysis from Veteran Administration Hospital (USA), only 77 (0.07%) of 100,453 cases reviewed, were reported to have cutaneous metastasis with average survival of 7.5 months.[4] This sort of rarity leads to misdiagnosis of skin lesions, more so when skin metastasis pre- or post-dates the malignancy. Review of the literature revealed 23 case reports of gall bladder carcinoma metastasizing to skin [Table 1]. Majority of the reported

Table 1: Reported Cases of Carcinoma Gall bladder metastasizing to skin (1961-2013)

Year	Author (Ref.)	Age	Country	Sex	Site of mets	Timing of skin lesion	Extent of skin involvement	Survival
1961	Tongco *et al*. (American Journal of Surgery. 1961;102:90-93)	NA	NA	NA	NA	NA	NA	NA
1982	Padilla *et al*. (Arch Dermatol. 1982;118 (7):515-7)	74	NA	F	Skin	NA	NA	NA
1993	Srinivasan *et al*. (Acta Cytol. 1993;37 (6):894-8)	NA	India	NA	Skin	At presentation	NA	NA
1995	Krunic *et al*. (Int J Dermatol. 1995;34 (5):360-2)	45	Yugoslavia	M	Skin	NA	NA	5 months
1998	Bardaji *et al*. (Hepatogastroenterology. 1998 45 (22):930-1)	75	Spain	F	Skin	NA	NA	NA
1999	Tamura *et al*. (Japanese Journal of Gastroenterological surgery online journal. 1999;32:2124-2128)	75	Japan	F	Skin	11 months later	Single	NA
2003	Motohiro *et al*. (Rinsho Derma (Tokyo) 2003;45:1253-1257)	62	Japan	M	Skin	1 year and 5 months later	Single	NA
2004	Pasricha *et al*. (Clin Oncol (R Coll Radiol) 2004;16 (7):502-3)	47	India	F	Skin	8 months after cholecystectomy	Multiple	Few months
2004	Wollina *et al*. (Acta Dermatoven APA 2004;13:79-84)	67	Germany	M	Scalp and supraclavicular fossa	NA	NA	NA
2006	Kaur *et al*. (Indian Journal of Dermatology, Venereology and Leprology. 2006;72 (1):64-66)	42	India	F	Skin	At presentation	Single	NA
2006	Kamisawa *et al*. (Journal of Gastroenterology and Hepatology. 2006;21:620)	84	Japan	M	Skin - zosteriform	4 years later	Multiple	4 months
2007	Krunic *et al*. (Australas J Dermatol. 2007;48 (3):187-9)	38	USA	M	Skin, face scalp, perianal	1 year later	Multiple	20 months post diagnosis - alive
2009	Mukhia *et al*. (J Nepal Med Assoc 2009;48 (176):318-20)	40	Nepal	F	Skin, thigh	At presentation	Multiple	NA
2009	Garg *et al*. (Hepatobiliary Pancreat Dis Int 2009;8:209-211)	42	India	F	Skin, breast	At presentation	Multiple	3 weeks

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Table 1: Contd

Year	Author (Ref.)	Age	Country	Sex	Site of mets	Timing of skin lesion	Extent of skin involvement	Survival
2009	Pushkar *et al*. (J Cytol. 2009; 26 (3):109-10)	42	India	F	Skin, breast	Few months later	Multiple	NA
2009	Pushkar *et al*. (J Cytol. 2009;26 (3):109-10)	51	India	M	Skin (umbilical region)	At presentation	Single	NA
2010	Karagulle *et al*. (Cilt 2009;26:162-164)	50	Turkey	F	Skin and bone	33 months later	Single	NA
2010	Chopra *et al*. (Indian Journal of Dermatology, Venereology, and Leprology. 2010;76:125-131)	55	India	F	Skin	6 months after radiation and chemotherapy	NA	NA
2010	Kumar *et al*. (Journal of Pakistan Association of Dermatologists 2010;20:232-237)	65	India	M	Forehead, trunk, extremities	At presentation	Multiple	NA
2012	Kumar *et al*. (BMJ Case Reports 2012;10.1136/bcr. 02.2012.5777.)	45	India	M	FNAC site on abdomen	1 month later	Single	Alive on supportive care
2012	Kumar *et al*. (J Cytol. 2012;29:277-278)	40	India	F	Scalp	At presentation	Multiple	NA
2013	Jeyaraj *et al*. (Rare Tumors 2013;5:e7)	74	USA	F	Skin–trunk	12-14 weeks later	Serially - multiple	25 months post diagnosis and alive
2013	Tanriverdi *et al*. (Ann Dermatol 2013;25:99-103)	70	Turkey	M	Skin–trunk	7 months later	Multiple	4 months
2013	Our case	76	India	F	Skin–trunk	At presentation	Multiple	7.5 months

F: Female, M: Male, NA: Not available, FNAC: Fine needle aspiration cytology

cases are from Northern India. More than 50% are females with the median age of 53 years. Among reported Indian patients 70% are females and the median age was lower at 46 years. Most of the reported patients presented to the physician with skin lesions as their primary symptom. Cases with umbilical metastasis (Sister Mary Joseph nodule) alone were excluded as we believe that the mechanism is different. The generalized dermatological metastasis is likely due to hematogenous spread, however in umbilical metastasis direct, hematogenous and lymphatic spread occurs. The skin metastasis generally occurs on the chest and abdomen and is rare in the extremities, neck, back and scalp.[5] Single metastatic lesions can closely simulate a benign cyst, keratoacanthoma, basal cell carcinoma or melanoma. The other differentials may include pyogenic granuloma, granular cell tumor, a benign subcutaneous nodule and cutaneous angiosarcoma. Certain metastatic tumors may closely simulate skin primary tumors, including metastatic small cell carcinoma as Merkel cell carcinoma, metastatic systemic sarcoma as primary skin sarcoma, papillary thyroid carcinoma as primary papillary adnexal tumors, clear cell renal cell carcinoma as either sebaceous carcinoma or clear cell hidradenoma and metastatic mucinous carcinoma as primary cutaneous mucinous carcinoma. Nodular metastatic lesions are easily and often misdiagnosed as simple cysts or benign connective tissue lesions. Therefore, atypical or persistent nodular lesions in patients with a history of systemic malignancy should be considered for biopsy to rule out metastasis.[6]

The intent of treatment in a patient with a Stage IV carcinoma gall bladder is palliative; however, the treatment (chemotherapy or best supportive care) for symptom control would definitely provide the patient a better quality-of-life if the diagnosis is made early.

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