Original Article

Spectrum of Malignant Transformation in Marjolins Ulcer: Our Experience of This Rare Phenomenon

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ABSTRACT

Background & Objective: **Chronic non healing ulcers or scar undergoing malignant transformation is a rare phenomenon with an estimated incidence of 2%. Though, numerous predisposing factors have been identified, still it is rarely diagnosed and commonly mistaken for a benign condition. The objective of this study was to verify the efficacy of the Fine Needle Aspiration Cytology/ Scrape cytology of chronic non healing ulcers, and its use in the early detection of the malignant transformation, thereby facilitating early management.**

Methods: **A total of 10 cases of chronic non healing ulcer with malignant transformation were included in the study where the initial diagnosis was made on fine needle aspiration cytology/ scrape cytology and later on confirmed on histopathology.**

Results: **Squamous cell carcinoma (7 cases), acantholytic variant of squamous cell carcinoma (1 case), malignant fibrous histiocytoma (1 case) and carcinosarcoma (1 case) was seen. A 100% concordance with histopathology was seen in squamous cell carcinoma cases. Because of the rarity of the case and unusual transformation, high grade pleomorphic spindle cell carcinoma was the cytological diagnosis in case of malignant fibrous histiocytoma.**

Conclusion: **Marjolin ulcer arising out of chronic non healing ulcers can prove to be a precursor of any different kind of malignancies. fine needle aspiration cytology/scrape cytology can be used as a first line diagnostic modality for the early diagnosis as it is a fast and safe method with high rate of accuracy, sensitivity and specificity.**

Keywords: **Skin Ulcer, Cancer, Fine Needle Aspiration, Cytology**

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Introduction

Chronic cutaneous ulcers are common in the developing countries like India, especially in rural areas with poor living conditions" (1)**.** Malignant neoplasm arising in these chronic, non-healing ulcers is known as Marjolin's ulcer. Da Costa in 1903 first coined the term "Marjolin's ulcer", in tumours arising from simple leg ulcers after "J N Marjolin" who first reported the development of tumors arising in burn scars of long duration in 1828 (2). Two years later, Dupuytren reported these tumours arising out of chronic ulcer to be of malignant nature (3). Marjolin's ulcer no longer refers only to carcinomas secondary to burns and is classified as a malignancy that arises from previously traumatized, chronically inflamed, or scarred skin. It has been reported in relation to osteomyelitis, venous stasis ulcer, tropical ulcers, chronic decubitus ulcer, frostbite, pilonidal sinus, vaccination site, urinary fistula, hidradenitis suppurativa, skin graft donor site, gunshot wounds, puncture wounds, dog bites, and lupus rash (4). Two variants are known, one is acute where cancer occurs within 1 year from the date of injury, and a chronic form in which malignant change is seen after 1 year from the beginning, with a time range of 1 – 75 years (5).

The exact mechanism of malignant transformation of Marjolin's ulcer remains unclear and controversial. Several theories including the toxin, chronic irritation, traumatic epithelial elements implantation, heredity, immunologic privileged site, co-carcinogen, ultraviolet rays, initiation and promotion and environmental and genetic interaction theories have been reported to explain the malignant transformation (6). When it occur in post burn contractures it is often around the region of maximum tension which undergoes repeated breakdown such as the popliteal fossa and cubital fossa (7).

Despite the numerous risk factors, this oncological syndrome is rarely diagnosed and commonly mistaken, and may often be overlooked. A definitive diagnosis of the malignant transformation is made by histological examination of tissue sections. Frozen section biopsy has been widely used for intraoperative diagnosis and evaluation of surgical excision safety margins (8). However, both the methods of diagnosis is time consuming, whereas cytology is a fast and reliable alternative with 98.7% accuracy, 98% sensitivity and 100% specificity in the intraoperative diagnosis of Marjolin ulcers (9).

Ten unique cases of chronic non healing ulcer with malignant transformation were studied and analyzed in this study, where prompt diagnosis on FNAC/ scrape cytology had lead to early therapeutic intervention and thus, decreasing morbidity and mortality associated with the delayed diagnosis. The uniqueness of the cases lies in the fact that malignant transformation has occurred within ten years of the occurrence of non healing ulcer with two of them being the acute form of Marjolin ulcer, and also varied cytomorphology along with histopathology was noted amongst a few cases.

Materials and Methods

This is an observational retrospective as well as prospective study of four years duration from April 2008 to March 2012, done at the Department of Pathology, Burdwan Medical College. FNAC/ scrape cytology was done in case of chronic non healing ulcers presenting in the out-patient department. A total of 10 cases of chronic non healing ulcer with malignant transformation were included in the study where the initial diagnosis was made on FNAC/scrape cytology and later on confirmed on histopathology.

Study cases i.e. FNAC smears or scrape cytology smears were retrieved from the records along with patient's personal details and clinical information. Patients fulfilling the following inclusion criteria were selected for the study

a) presence of chronic non healing ulcer

b)History of trauma, burns, venous insufficiency, poor personnel hygiene, constant irritation,

osteomyelitis etc leading to non healing ulcer
c)Non diabetic patients
Histopathological diagnosis was available in all the cases. FNAC/scrape cytology was performed from multiple sites of the ulcer especially the edges and the base of the ulcer. The smears were stained by Leishman & Giemsa along with Haematoxylin & Eosin. All the smears were examined by at least two expert cytopathologists and the results were compared with the histopathological diagnosis. Immunohistochemistry was also performed in cases of unusual histopathological diagnosis to support and confirm the diagnosis.

Results

A total of 10 patients with history of chronic non healing ulcer were included in the study during a period of four years with a male to female ratio of 1:1. The median age was 30 years with an age range of 19-53 years. The majority of the patients i.e. 70% were younger than 40 years.
History of Burn scar was the most common presentation representing 60% of the total cases followed by post traumatic scar (2 cases) and one case each of post operative scar and osteomyelitis sinus scar. The mean latent period between the initial injury and development of Marjolin's ulcer was 2.83 years with two cases showing malignant transformation within one year of initial injury and hence designated as acute form of Marjolin ulcer.
Most of the patients presented with solitary chronic non healing ulcer at the site of injury, with a history of gradual increase in size and pain. History of Burn in six cases, trauma in two cases, surgery in one case and osteomyelitis in another was found to be etiological factors in the causation of non healing ulcer. Macroscopically, all the cases had ulcerative lesion measuring more than 5 cm in greatest dimensions except non healing ulcer of the osteomyelitis scar. The ulcer with malignant transformation had everted margin, and evidence of necrosis as compared to the benign chronic cutaneous ulcer (Fig.1). Causative factors, lag period, FNAC findings and histopathological diagnosis along with immonohistochemistry of all the cases is described in Table 1.

Table 1- Morphological patterns of malignancies arising in marjolin's ulcer

No.	Type of lesion	Age (yr)	Sex	Lag period (yr)	FNAC*	Histopathology	IHC**
1	Burn ulcer	39	F	4	SCC***	SCC	_
2	Burn ulcer	20	F	1	SCC	SCC	_
3	Stick injury	45	M	5	SCC	SCC	_
4	Post operative scar	35	M	2	SCC with acini formation	Acantholytic variant of SCC.	CK **** Pos, Vimentin Neg
5	Burn ulcer	28	M	2	SCC	SCC	_
6	Burn ulcer	53	M	1	SCC	SCC	_
7	Osteomyelitic sinus	19	F	2	Spindle cell lesion	MFH	CK Neg , Vimentin Pos
8	Burn scar	30	M	10	SCC	SCC	_
9	Post traumatic scar	25	F	7	SCC with spindle cells.	Carcinosarcoma.	CK Pos, Vimentin Pos
10	Burn scar	40	F	2	SCC	SCC	_

* Fine Niddle Aspiration Cytology
** Immunohistochemistry
*** Squamous Cell Carcinoma
**** Cytokeratin

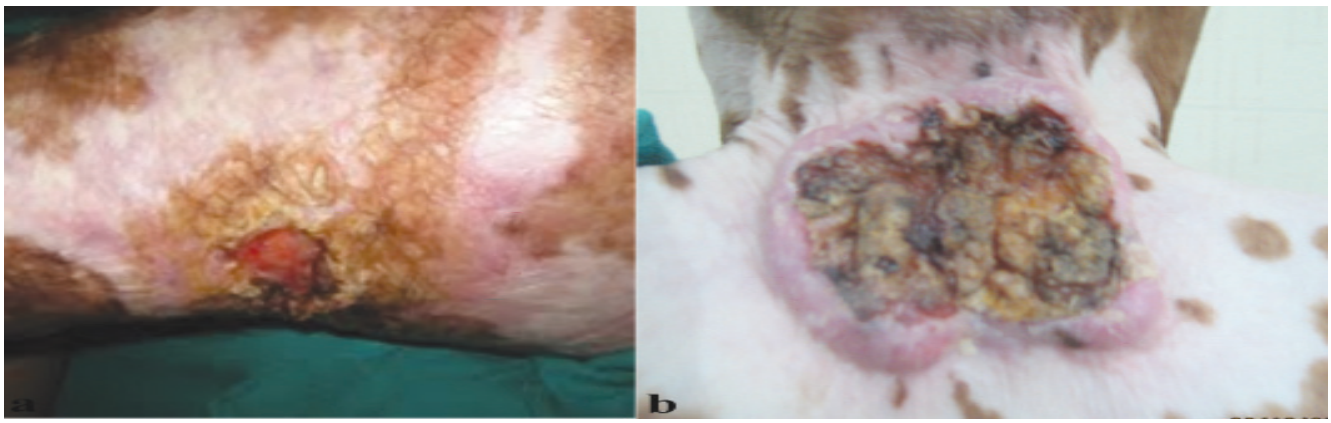

Fig. 1: Comparison of two burn ulcers. Fig. 1a represents a benign ulcer and Fig 1b represents malignant one with rolled out everted margins, large size and evidence of necrosis (Original)

Microscopically, all the cases showed wide degree of variation and diversity. The FNAC/scrape smears were highly cellular in all the cases with presence of dysplastic and malignant squamous epithelial cells in all the cases (Fig. 2) except one where only neoplastic spindle cells were seen. A cytomorphological diagnosis of Squamous cell carcinoma was made in all cases except one where a diagnosis of highly pleomorphic Spindle cell sarcoma was given (Fig. 3). Among cases of squamous cell carcinoma, one of the case exhibited acini formation by malignant epithelial cells in fine needle aspiration cytology smears, which mimicked adenocarcinoma. But on histopathological examination, the same case turned out to be acantholytic variant of squamous cell carcinoma showing central dyscohesiveness and pseudoglandular architecture.

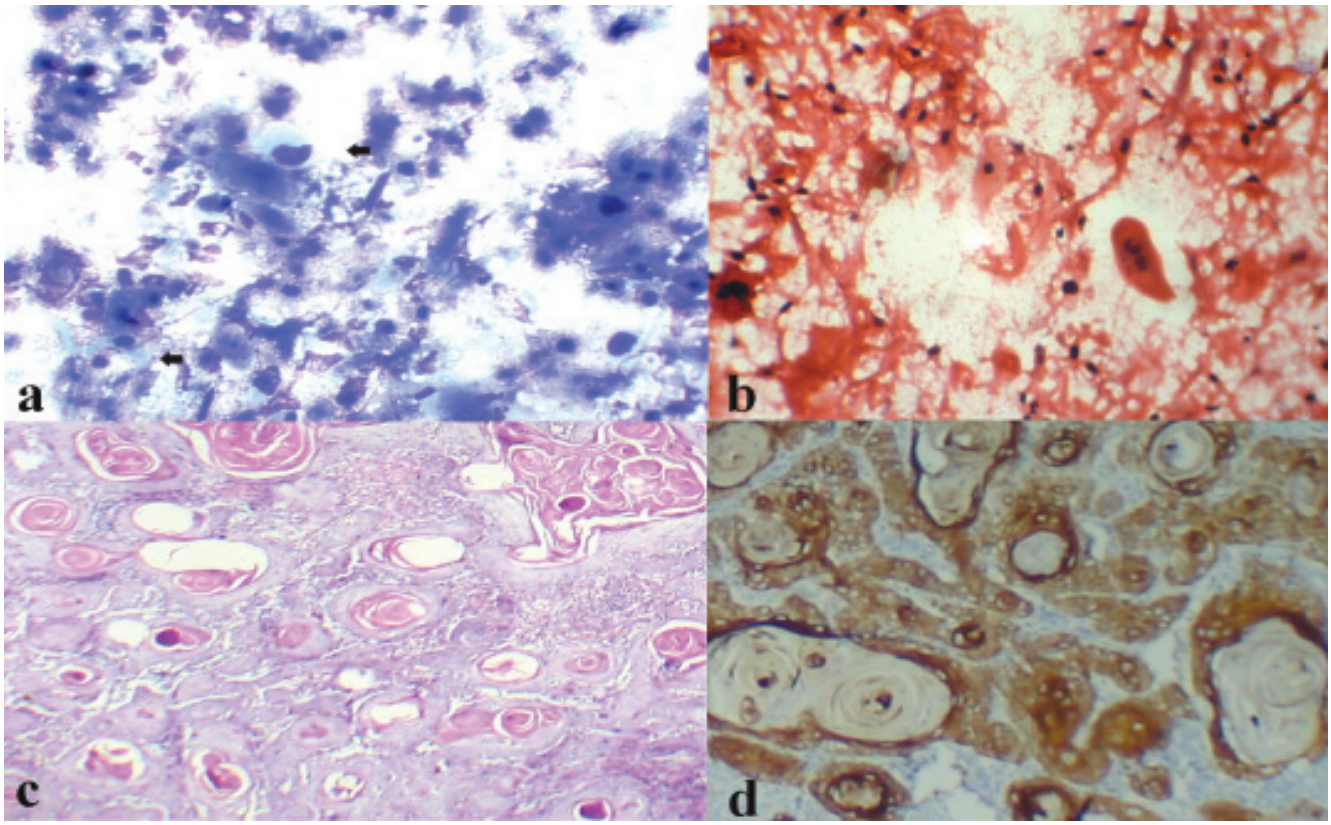

Fig. 2: Cellular smears showing malignant squamous cells (Fig. 2a, 2b, MGG and H&E, ×100) Section shows sheets and islands of malignant squamous cells with keratin pearl formation (Fig. 2c, H&E, ×400) Cytokeratin positive malignant squamous cells (Fig. 2d)

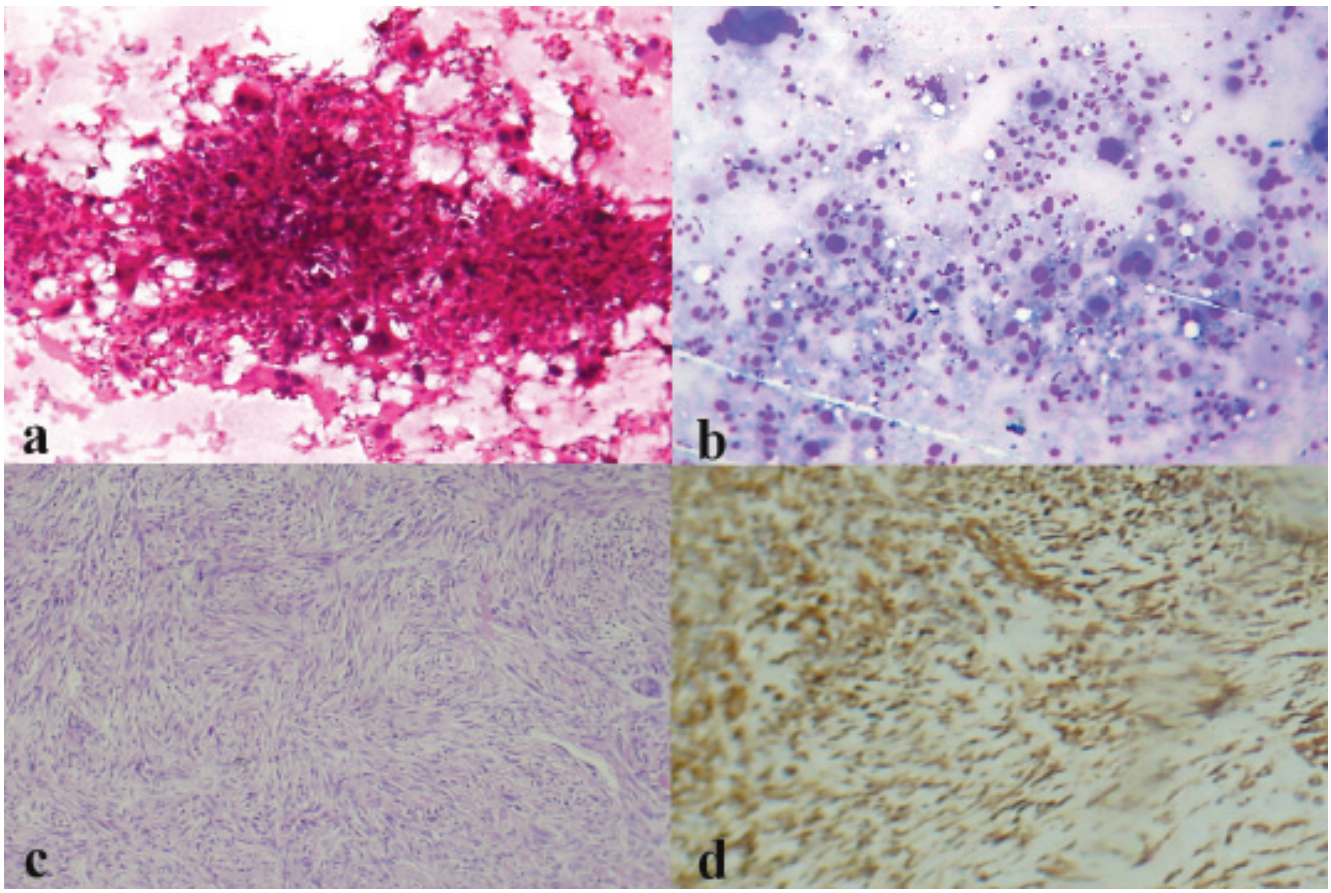

Fig. 3: Highly pleomorphic spindle cell lesion, with multinucleated giant cell (Fig. a,b) storiform pattern on histopathology (Fig. c) and vimentin positive spindle cell

Another interesting case diagnosed cytologically as squamous cell carcinoma turned out to be carcinosarcoma after histopathological diagnosis, showing dysplastic squamous cells in sheets with pearl formation, invading the stroma, underneath which lies hypercellular zone of dysplastic spindle cells arranged in whorls & fascicles (Fig. 4c). The same case on cytomorphology had shown presence of a few scattered neoplastic spindle cells amidst neoplstic squamous epithelial cells (Fig. 4 a, b). The neoplastic spindle cells exhibited vimentin positivity, whereas the squamous cells showed positive reaction for cytokeratin.

Highly pleomorphic spindle cell sarcoma on FNAC in a case of non healing ulcer developed at the site of osteomyelitis was diagnosed as malignant fibrous histiocytoma on histopathology (Fig. 3). On FNAC, smears from the same case were highly cellular with predominantly oval to spindle cells exhibiting high degree of cellular and nuclear pleomorphism and at places, storiform configuration. Another interesting fact observed with the present study was that all the cases of Squamous cell carcinoma occurred where original injury was burn ulcer, whereas malignant fibroushistiocytoma and carcinosarcoma developed in cases of osteomyelitis and post traumatic scar ulcer respectively. Acantholytic variant of squamous cell carcinoma has also developed in a case of post operative scar.

Discussion

Chronic non healing ulcers or scar undergoing malignant transformation is a rare phenomenon with an estimated incidence of 2% (10). Moon *et al*. suggested the incidence for malignant tumors in chronic leg ulcers to be around 2·2% with an incidence for Squamous cell carcinoma (SCC) of 0.4% being significantly higher than the incidence for SCC in the normal population

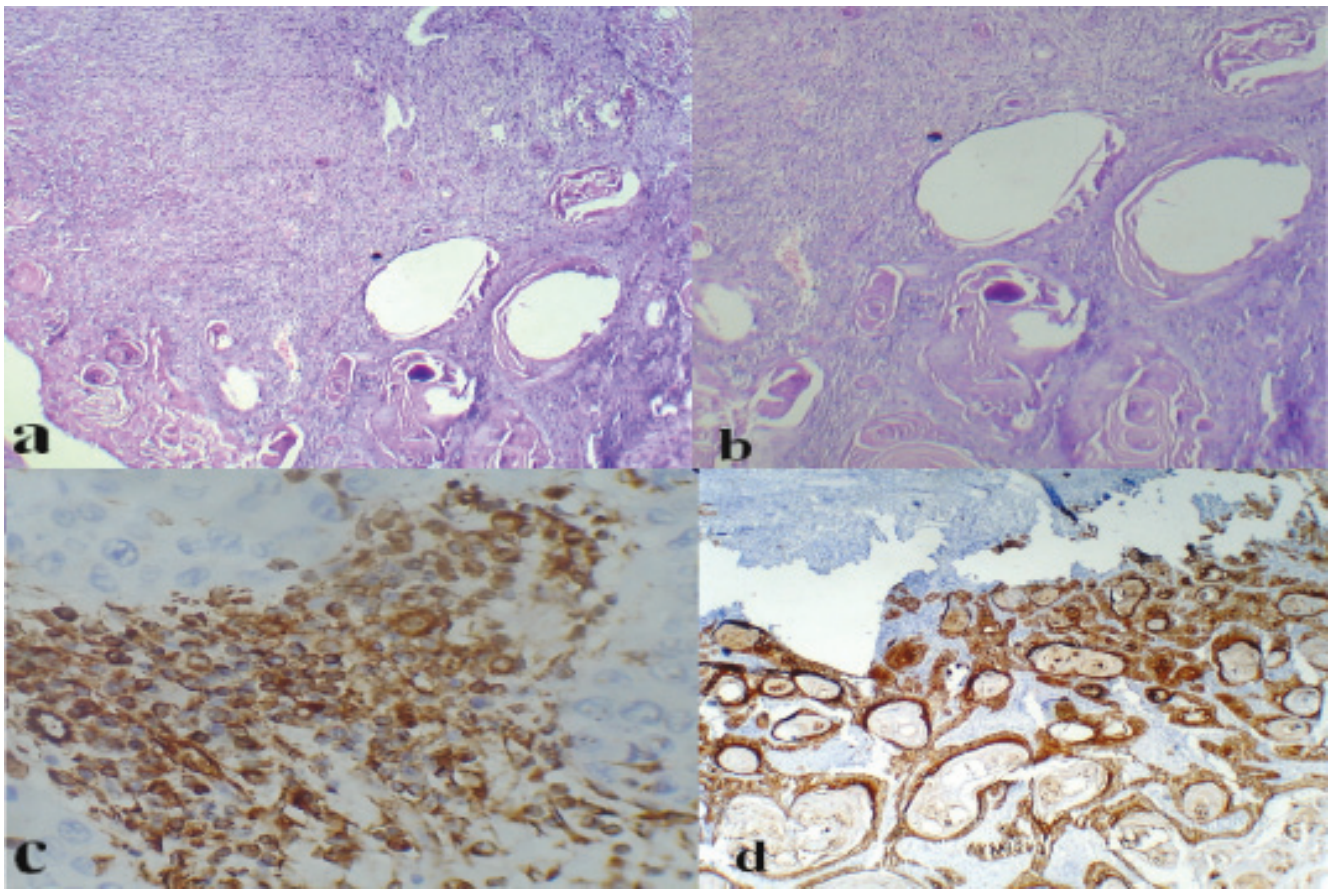

Fig. 4: Fig. a and Fig. b represents sarcomatous and carcinomatous portions of carcinosarcoma.Vimentin positive cells and cytokeratin positive squamous cells on Fig. c and Fig. d respectively

(11). Nthumba had reported incidence of 97.6% squamous cell carcinomas, 1.8% sarcomas, and 0.6% malignant melanoma in chronic ulcers where burn scars, chronic ulcers, osteomyelitis, and "other" ulcers constituted 49%, 42%, 5.4% and 3.6%, respectively. He also reported a mean latent period 16 of years (12). Aydogdu *et al.* found that the lower extremities (43.7%), upper extremities (22.4%), head (22.4%) and trunk (11.5%) are the most frequent locations involved (7). The present study corroborated well with Nthumba, in maximum numbers of cases exhibiting malignant transformation into SCC and only two cases of sarcoma.

Histologically, most of the malignant transformation in chronic ulcers is squamous cell carcinoma followed by Basal cell carcinoma (13). Malignant melanoma, sarcomas (among them: fibrosarcoma, liposarcoma, dermatofibrosarcoma, protuberans, mesenchymal tumor), mixed tumors like SCC-BCC, SCC-melanoma are less frequently seen in Marjolin's ulcer (8).

There is a lag period between the development of Marjolin's ulcer in a scar tissue and the time of injury with observed latency being inversely proportional to the patients' age. Malignant transformation is delayed in younger injury victims. The older the patient at the time of injury, the shorter the lag period (14). Non healing ulcers enlarging in circumference with elevated and indurated boarders, foul smelling, painful with exudates & bloody drainage and bone destruction radiologically suggest a malignant transformation (8). All the ten cases have shown malignant transformation within 10 years of initial injury, and also most of the patients were less than 40 years of the age in the present study. Though no radiological evidence of bone destruction was found in any of the cases, history of gradual increase in size with evidence of necrosis at the ulcer base and gradually increasing pain was present in all the cases.

Development of Malignant Fibrous Histiocytoma

in a chronic burn scar is an exceedingly rare occurrence with only a rare case reported in the literature. Early excision is needed as it has high propensity for early and distant spread (15). Similarly, carcinosarcomas are rare neoplasms, rarely seen developing in chronic ulcer. Moon *et al.* reported a case of carcinosarcoma in a 31-year-old young man with burn scar at the dorsum of the ankle which histopathologically was a mixture of squamous cell carcinoma and malignant fibrous histiocytoma. They did excision biopsy with wide skin margin and applied split thickness skin graft (11). However, since both the above sarcomatous change is very rare in Marjolin's ulcer, not much is known about the prognosis and best treatment modality even with extensive search of the literature. Both the cases in the present study were treated with wide excision and skin graft with no evidence of recurrence till date. Early detection of these cases with the help of FNAC had helped the clinicians to impart an early surgical intervention.

Histopathological and cytomorphological diagnosis of malignant transformation in Marjolin's ulcer does not pose much of a problem and ancilliary technique like immunohistochemistry is required only in cases of unusual neoplasm. Kim *et al* did immunohistochemistry using high-molecular-weight keratins and vimentin in cases of malignant transformation in marjolin's ulcer and compared it with those of primary SCC and BCC. They found that Marjolin's ulcer-SCC has largely high-molecular-weight keratins along with a wide range of reactivity with Vimentin (V9). However, neoplastic cells of five of the six primary SCC and five cases of BCC were negative for V9. These findings suggest that neoplastic cells of SCC-MU contain vimentin in higher frequency than in the more usual SCC (16). In the present study, IHC was done only in the cases of Acantholytic variant of SCC, MFH and carcinosarcoma using cytokeratin and vimentin. Except MFH, both acantholytic variant of SCC and carcinosarcoma showed reactivity with both the markers. Immunohistochemistry couldn't be done in all the cases because of characteristic morphological pattern of the cases and also poor socio-economic condition of the patients.

SCCs that arise from Marjolin's ulcers are aggressive and have high metastatic potential (30% risk) compared to 3% risk in SCCs originating in normal skin (17).The treatment of Marjolin's ulcers requires multidisciplinary approach and includes wide local excision, block dissection of the regional nodes, amputation in advanced lesions of limbs, radiotherapy and chemotherapy given either as neo or adjuvant therapy (8). Amputation is done only in cases of extensive involvement and advanced lesions (18). To prevent the malignant transformation, recurring ulcers should be excised even if they are not malignant and skin grafting should be done (19). Unfortunately diagnosis is often delayed and 30% cases have enlarged lymph nodes with possible metastasis at the time of presentation (8).

Prognosis depends on local extension of disease, its anatomical location & presence or absence of lymph node metastasis (1). Prognosis for patients with Marjolin's ulcer ranges from 65% to 75% for 3 years survival and with metastasis the 3 year survival rate falls to 35 to 50% (9). Basal cell carcinoma has relatively better prognosis than squamous cell carcinoma (19).

Conclusion

A high level of suspicion in early detection of malignant changes in chronic ulcers is important whenever ulcers fail to respond to conventional therapies. Marjolin ulcer arising out of various chronic wounds can prove to be a precursor of any different kind of malignancies – carcinoma mainly squamous in nature, sarcoma, or carcinosarcoma. FNAC/scrape cytology can be used as a first line diagnostic modality for the early diagnosis as it is a fast and safe method for the early detection of malignant transformation with high rate of accuracy, sensitivity and specificity.

Acknowledgment

The authors declare that there is no conflict of interests.

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