Merkel cell carcinoma of the abdominal wall

Vandana L. Gaopande, Avinash R. Joshi, Siddhi G. S. Khandeparkar, Sanjay D. Deshmukh

Department of Pathology, Smt Kashibai Navale Medical College and General Hospital, Pune, Maharashtra, India

ABSTRACT

Merkel cell carcinoma also known as neuroendocrine carcinoma of the skin is a very rare skin tumor. It commonly presents in the old age and the common sites are head, neck and extremities. The diagnosis requires histopathological examination with immunohistochemical correlation. We report a case of Merkel cell carcinoma stage IIIB with bilateral inguinal lymphadenopathy that on FNAB showed metastatic deposits of the tumor.

Key words: Immunohistochemistry, Merkel cell carcinoma, Merkel cell polyoma virus

Access this article online

Website: www.idoj.in

DOI: 10.4103/2229-5178.160262

Quick Response Code:

Address for correspondence:
Dr. Vandana L Gaopande, Department of Pathology, Smt Kashibai Navale Medical College and General Hospital, Off Katraj Bypass Highway Flyover, Narhe, Ambegaon, Pune - 411 041, Maharashtra, India.
E-mail: vandanagaopande@gmail.com

INTRODUCTION

Merkel cell carcinoma (MCC) also known as neuroendocrine carcinoma of skin is an uncommon tumor of the skin that accounts for a small fraction of cutaneous malignancies. However, the age-adapted incidence appears to have tripled between 1986 to 2001, with a statistically significant annual increase of 8%.[1] It presents as a rapidly growing skin nodule usually on the sun-exposed parts of the body, predominantly in males, with a mean age of 70 years at the time of diagnosis.[2] It is an aggressive tumor and shows a tendency for local recurrence, lymph node involvement, and distant metastasis. The prognosis is poor. We herein present a case of this rare tumor with immunohistochemical correlation.

CASE REPORT

A 70-year-old woman, a known case of senile dementia presented to the surgery outpatient department with lump on her abdominal skin since six months and discharge through the lump since two weeks. Her temperature, pulse rate, and blood pressure were within normal limits. The abdomen was soft and nontender. Liver and spleen were not palpable. An infraumbilical midline scar elicited a history of hysterectomy 30 years back for dysfunctional uterine bleeding. There was no history indicating exposure to radiation. There was no history of immunosuppressive treatment, and enzyme-linked immunosorbent assay for HIV was negative. A mass was noted on the abdominal wall below and to the right side of umbilicus. It was 8 × 8 cm in size, soft, nontender, with surface ulceration and bluish in color. She also had bilateral inguinal lymphadenopathy. She was admitted to the surgical ward and a fine-needle aspiration biopsy (FNAB) of the abdominal lump was done. The FNAB showed cellular smears consisting of small round cells arranged in groups, clusters, as well as singly scattered [Figure 1]. The cells had large hyperchromatic nuclei, and occasional abnormal mitotic figures were seen. The background was proteinaceous. A differential diagnosis of small cell carcinoma, lymphoma, and neuroendocrine carcinoma was offered. FNAB of inguinal lymph nodes showed metastasis of the tumor with similar microscopic features. A wide local excision of the abdominal lump was done under general anesthesia after routine hematological and biochemical investigations. Intraoperatively, the lump was mainly subcutaneous extending up to and involving the rectus sheath for an area of approximately 2 cm diameter. It was not found to involve the peritoneum. Gross examination of the surgical specimen received in pathology department consisted of a skin covered bluish, firm mass measuring 8 × 7× 5 cm. An ulceroproliferative, irregular growth was seen fungating through skin measuring 4.5 × 4.5 × 3 cm. Cut surface of the tumor was greyish white and hemorrhagic at places. The tumor was infiltrating the subcutaneous tissue [Figure 2]. Microscopic examination showed a poorly circumscribed tumor in the reticular dermis of skin [Figure 3a] infiltrating the subcutaneous tissue. Surface ulceration was seen. The tumor cells were small having a large

hyperchromatic nucleus with a small rim of cytoplasm. The nuclei showed a finely granular chromatin with inconspicuous nucleoli. The cells were arranged in nests, chords, and trabeculae as well as in sheets. [Figure 3b] Fibrous septa containing blood vessels were seen. Tumor necrosis was noted. All margins except the basal surgical margin were free of tumor. The basal margin showed tumor infiltrates. On immunohistochemistry Cytokeratin 20 (CK20, Dako clone Ks-20.8), Synaptophysin (SYN, Novocastra clone 27G12), and neuron-specific enolase (NSE, Novocastra clone 5E2) were positive and showed cytoplasmic positivity [Figure 4]. A diagnosis of Merkel cell carcinoma, stage IIIB was offered.

DISCUSSION

The first description of MCC can be traced to Toker (1972) who called it trabecular carcinoma of the skin.[3] Tang and Toker (1978) found dense core granules in the cytoplasm of the tumor cells by electron microscopy. This fact led to the hypothesis that this tumor arises from Merkel cells.[4] However, some authors believe that MCC arises from pleuripotent stem cells of the skin.[5] The name Merkel cell carcinoma was proposed by De Wolff-Peeters in 1980 and is the most accepted term.[6] In mammals, Merkel cells (MC) are found in the basal layer of the skin and mucosa either as single cells or in clusters. Clusters are in close vicinity of nerve terminals forming mechanoreceptors.[7] They also function as neuroendocrine cells, secreting metenkephalin, vasoactive intestinal polypeptide, substance P, and calcitonin gene-related peptide to transmit or transduce chemical information.[8] MC are difficult to find on light microscopy. Their morphology can be seen under electron microscopy whereby they are seen to have lobulated nuclei, a loose cytoskeletal network of intermediate filaments, dense core cytoplasmic granules, and spine-like microvilli protruding from the surface into invaginations in surrounding keratinocytes.[9]

A nation-wide incidence of MCC was extracted from the Danish Cancer Registry by Lyhne *et al*. for the period 1986–2003. Incidence rates had increased 5.4 times over the period of 18 years.[10] In Surveillance, Epidemiology and End Results (SEER) program data from 1986 to 2001, the age-adjusted US annual incidence of MCC tripled from 0.15 to 0.44 per 1,00,000, which is an increase of

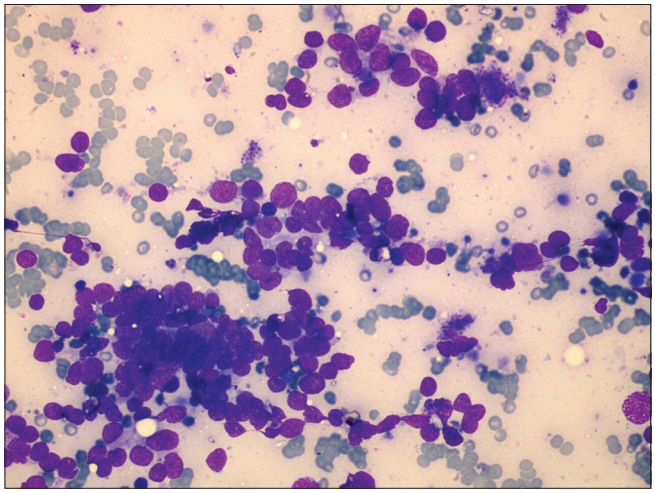

Figure 1: Groups and clusters of small round cells having hyperchromatic nuclei

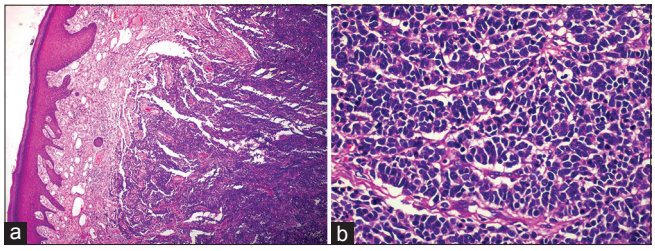

Figure 3: (a) The tumor in the reticular dermis of skin (hematoxylin and eosin, ×40), (b) showing the small cells arranged in trabeculae showing salt and pepper chromatin (hematoxylin and eosin, ×400)

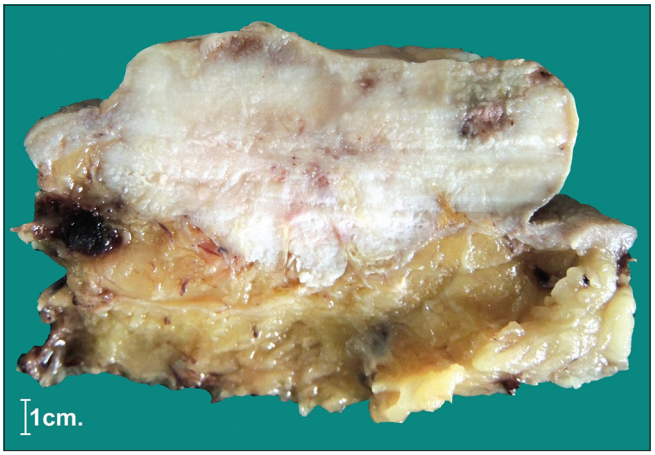

Figure 2: Gross specimen of the tumor showing an exophytic growth, infiltrating into the subcutaneous fat

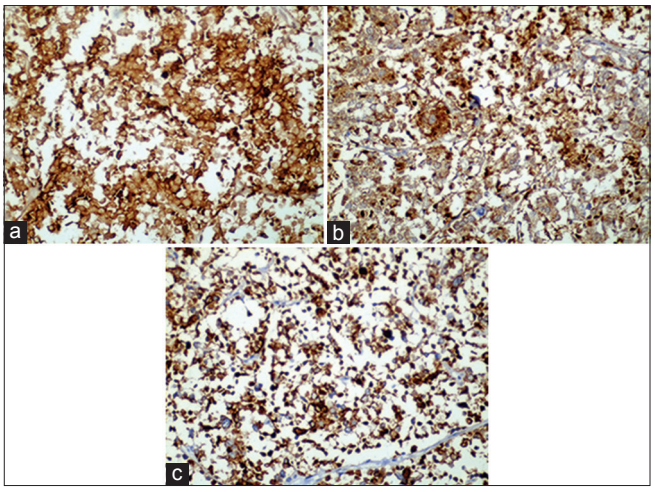

Figure 4: (a) Perinuclear dot-like immunoreactivity for CK20 (b) cytoplasmic immunoreactivity for neurone-specific enolase, (c) cytoplasmic immunoreactivity for synaptophysin (×400)

8.08% per year.[11] About 1500 new cases of MCC were expected in the United States in 2007. Incidence is greater in whites than in blacks and slightly higher in males than in females.[11] The increase in incidence may reflect an actual increase and/or more accurate diagnostic pathology tools, increased awareness of MCC, an aging population, increased sun exposure in susceptible population, and improved registry tools.

MCC typically develops as a painless, nontender rapidly growing nodule or plaque, mostly located on sun-exposed areas of the body of an elderly person. The nodule is solitary, firm, flesh colored-to-reddish-blue, having a smooth shiny surface. It is found to be associated with immunosuppression in 10% cases. The reported age range has been from 7 to 95 years and majority of patients are older than 65 years.[12] The male: female ratio varies among studies. The skin of head and neck is affected in 50% cases, extremities in 40%, and trunk and mucosa in 10%.[13] The clinical differential diagnosis includes basal cell carcinoma, squamous cell carcinoma, pyogenic granuloma, keratoacanthoma, amelanotic melanoma, benign cyst, adenexal tumor, lymphoma, and metastatic carcinoma.

The tumor is seen in the dermis, infiltrating into the subcutaneous tissue. The epidermis is usually not involved. Rare cases showing epidermotropism or those confined to epidermis have been reported.[12] Three histopathological patterns have been described. (1) Trabecular type with connective tissue separating interconnecting cellular trabeculae, (2) Intermediate cell type, which is most common, consisting of solid nests with trabeculae at the periphery, and (3) Small cell type consisting of sheets of small cells with a diffusely infiltrative pattern.[12] These patterns may coexist in a single tumor. In the present case, the predominant pattern was of sheets of small round cells. The tumor cells are rounded, monomorphic, small to medium sized with scanty cytoplasm, round nuclei with inconspicuous nucleoli (blue cells). The nuclei have finely granular chromatin and may show the typical salt and pepper appearance. Aggregates of tumor cells sometimes produce a pseudorosette appearance. Mitosis may be prominent. An infiltrative margin is observed most commonly. A lymphocytic infiltrate may surround and/or infiltrate the tumor cells. Tumor necrosis may be seen. The tumor may show squamous, eccrine, leiomyomatous or melanocytic differentiation. Other malignant neoplasms such as actinic keratosis, Bowen disease, basal cell carcinoma, squamous cell carcinoma, and sweat gland tumors have been reported within or adjacent to lesions of MCC.[12] ACTH-producing MCC has been reported.[14] Ectopic Anti Diuretic Hormone secretion by a neuroendocrine tumor with MCC phenotype was recently reported.[15] Serum NSE may prove to be a useful tumor marker in MCC.[16]

Differential diagnosis

The histologic differential diagnosis includes malignant melanoma, lymphoma, and cutaneous small cell epithelial tumors such as small cell squamous cell carcinoma, basal cell carcinoma, sweat gland carcinoma, and metastatic neuroendocrine carcinoma.

Immunohistochemistry

MC demonstrate both epithelial and neuroendocrine markers. The loosely arranged intermediate filaments are stained by low molecular weight cytokeratins (CK) 8, 18, 19, and 20. CK20 in particular has been shown to be a highly specific marker for MC in normal skin where it is a diffuse cytoplasmic stain. The dense core granules of MC show immunoreactivity for neuroendocrine markers chromogranin, synaptophysin, and neuron-specific enolase. In 1992, Dr. Moll *et al*. found that CK20 expression was highly specific for MCC. It stains 80%–90% of all MCC in a characteristic paranuclear dot-like pattern, which is due to clumping of intermediate filaments.[17] Neurofilament immunostains are also positive in a paranuclear dot-like pattern in up to 95% of MCC.[18] MCC also frequently stain positive for neuroendocrine markers chromogranin, neuron-specific enolase, and synaptophysin. IHC helps to distinguish MCC from other small cell neoplasms of skin. Thyroid transcription factor-1 staining is useful to distinguish metastatic small cell carcinoma of lung from MCC. Leukocyte common antigen staining distinguishes the MCC from lymphoma. S-100 helps to distinguish MCC from melanoma.

Merkel cell polyoma virus (MCPyV) association: In 2008, Feng *et al*. studied MCC samples by digital transcriptome subtraction and detected a fusion transcript between a previously undescribed virus T antigen and a human receptor tyrosine phosphatase. Further investigation led to identification and sequence analysis of the 5387 base pair genome of a previously unknown polyomavirus that they called Merkel cell polyomavirus (MCPyV). MCPyV sequences were detected in 8 out of 10 (80%) MCC tumors but only 5 out of 59 (8%) control tissues from various body sites and 4 out of 25 (16%) control skin tissues. In 6 out of 8 MCPyV-positive MCCs, viral DNA was integrated within the tumor genome in a clonal pattern suggesting that viral infection and integration occurred before the clonal expansion of the tumor cells.[19] This suggested that MCPyV may be a contributing factor in pathogenesis of MCC. Since the publication of this study, additional studies have substantiated that approximately 80% of MCC contain MCPyV.[20] Sihto *et al*. reported that compared with MCPyV DNA–negative cancers, MCPyV DNA–positive cancers were more often located in a limb (40.7% vs 8.7%, $P = 0.015$) and less frequent in patients who had regional nodal metastases at diagnosis (6.6% vs 21.7%, $P = 0.043$). Patients with MCPyV DNA–positive tumors had better overall survival than those with MCPyV DNA–negative tumors

(5-year survival: 45.0% vs 13.0%, respectively; $P < 0.001$).[21] One recent study done to evaluate MCPyV seroprevalence and seroconversion among adult men at risk for HIV infection suggests that MCPyV infection is a highly prevalent infection among adults that is often asymptomatic.[22] Antibodies recognizing MCPyV large and small tumor-associated antigens are relatively specifically associated with MCC, do not effectively protect against disease progression, and may serve as a clinically useful indicator of disease status.[23]

It has been estimated that the risk of MCC increases 15-fold over the general population in immunosuppressed patients (chronic lymphoid leukemia, HIV infection, immunosuppressive treatment).[24] Intratumoral CD8 + was independently associated with improved survival in multivariate analysis.[25] Spontaneous regression has been reported in MCC, and the estimated rate of regression is 1.4%.[26] Paraneoplastic autoimmune neurologic disorders such as Lambert–Eaton myasthenic syndrome, brainstem encephalitis, and others have been observed in MCC.[27-30]

In 2010, American Joint Committee on Cancer released its first consensus staging system for MCC and is reported in the literature.[31] The present case was pT3N1bMx (over 5 cm maximum tumor dimension with macrometastasis in regional lymph nodes), stage IIIB.

Andea *et al*. evaluated retrospectively the following histologic features with regard to prognosis: Tumor thickness, microanatomic compartment involved by the tumor (dermis, subcutis, deeper), lymphovascular invasion, tumor-infiltrating lymphocytes, tumor necrosis, ulceration, and solar elastosis. They found that tumor architecture (nodular or infiltrative), tumor thickness, and lymphovascular invasion are independent predictors for survival along with tumor stage in patients of MCC.[32]

Treatment of MCC consists of surgery and radiotherapy. Current recommendations for surgical margin are based on clinical size of the primary tumor. They are tumor excision with 1 cm margins for tumors <2 cm in size and 2 cm margins for those >2 cm in size.[33] Sentinel lymph node biopsy (SLN) is currently recommended for all untreated, clinically node-negative primary MCC at the time of wide local excision. SLN biopsy is needed for proper staging of tumor and should be examined both by hematoxylin and eosin (H and E) stain and immunohistochemistry.[33] If SLN is positive complete lymph node dissection followed by radiotherapy is recommended. In case SLN is positive on immunohistochemistry only, then radiotherapy without lymph node dissection may be considered. MCC is radiosensitive and radiotherapy is currently used as an adjunct to surgery.[16] It is used as primary therapy only in inoperable cases and when the patient refuses surgery. In the present case, wide local excision with 2 cm margin along with regional lymph node dissection was done. The patient was then referred for radiotherapy. The patient was lost to follow up.

CONCLUSION

MCC is a rare malignancy of skin. Immunohistochemistry plays an important role in the diagnosis of MCC.

REFERENCES

1. Schrama, D, Ugurel, S, Becker JR. Merkel cell carcinoma. Current Opinion in Oncology 2012;24:141-9.
2. Jaeger T, Ring J, Andres C. Histological, immunohistological, and clinical features of Merkel cell carcinoma in correlation to Merkel cell polyomavirus status. J Skin Cancer 2012;2012: 983421.
3. Toker C. Trabecular carcinoma of the skin. Arch Dermatol 1972;105:107-10.
4. Tang CK, Toker C. Trabecular carcinoma of skin. An ultrastructural study. Cancer 1978;42:2311-21.
5. Koba S, Misago N, Nagase K, Tsuruta N, Inoue T, Ikeda S, *et al*. Triphasic differentiation of Merkel cell carcinoma in primary and metastatic lesions. J Cutan Pathol 2014;41:469-74.
6. De Wolff-Peeters C, Marien K, Mebis J, Desmet V. A cutaneous APUDoma or Merkel cell tumor? A morphologically recognizable tumor with a biological and histological malignant aspect in contrast with its clinical behavior. Cancer 1980;46:1810-6.
7. Halata Z, Grim M, Bauman KI. Friedrich Sigmund Merkel and his "Merkel cell", morphology, development, and physiology: Review and new results. Anat Rec A Discov Mol Cell Evol Biol 2003;271:225-39.
8. Tachibana T, Nawa T. Recent progress in studies on Merkel cell biology. Anat Sci Int 2002;77:26-33.
9. Munger BL. The intraepidermal innervations of the snout skin of the opossum. A light and electron microscope study, with observations on the nature of Merkel's Tastzellen. J Cell Biol 1965;26:79-97.
10. Lyhne D, Lock-Andersen J, Dahlstrøm K, Drzewiecki KT, Balslev E, Muhic A, *et al*. Rising incidence of Merkel cell carcinoma. J Plast Surg Hand Surg 2011;45:274-80.
11. Hodgson NC. Merkel cell carcinoma: Changing incidence trends. J Surg Oncol 2005;89:1-4.
12. Smith PD, Patterson JW. Merkel cell carcinoma (neuroendocrine carcinoma of the skin). Am J Clin Pathol 2001;115(Suppl):S68-78.
13. Cirillo F, Vismarra M, Cafaro I, Martinotti M. Merkel cell carcinoma: A retrospective study on 48 cases and review of literature. J Oncol 2012;2012:749030.
14. Anzai S, Sato T, Takayasu S, Asada Y, Terashi H, Takasaki S. Postoperative hyponatremia in a patient with ACTH-producing Merkel cell carcinoma. J Dermatol 2000;27:397-400.
15. Blondin NA, Vortmeyer AO, Harel NY. Paraneoplastic syndrome of inappropriate antidiuretic hormone mimicking limbic encephalitis. Arch Neurol 2011;68:1591-4.
16. Giannone L, Johnson DH, Grosh WW, Davis BW, Marangos PJ, Greco FA. Serum neuron-specific enolase in metastatic Merkel cell tumors. Med Pediatr Oncol 1985;13:357-62.
17. Moll R, Löwe A, Laufer J, Franke WW. Cytokeratin 20 in human carcinomas. A new histodiagnostic marker detected by monoclonal antibodies. Am J Pathol 1992;140:427-47.
18. McCalmont TH. Paranuclear dots of neurofilament reliably identify Merkel cell carcinoma. J Cutan Pathol 2010;37:821-3.
19. Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. Science 2008;319:1096-100.
20. Becker JC, Houben R, Ugurel S, Trefzer U, Pföhler C, Schrama D. MC polyomavirus is frequently present in Merkel cell carcinoma of European patients. J Invest Dermatol 2009;129:248-50.

21. Sihto H, Kukko H, Koljonen V, Sankila R, Böhling T, Joensuu H. Clinical factors associated with Merkel cell polyomavirus infection in Merkel cell carcinoma. J Natl Cancer Inst 2009;101:938-45.
22. Tolstov YL, Knauer A, Chen JG, Kensler TW, Kingsley LA, Moore PS, *et al*. Asymptomatic primary Merkel cell polyomavirus infection among adults. Emerg Infect Dis 2011;17:1371-80.
23. Paulson KG, Carter JJ, Johnson LG, Cahill KW, Iyer JG, Schrama D, *et al*. Antibodies to merkel cell polyomavirus T antigen oncoproteins reflect tumor burden in merkel cell carcinoma patients. Cancer Res 2010;70:8388-97.
24. Triozzi PL, Fernandez AP. The role of the immune response in merkel cell carcinoma. Cancers (Basel) 2013;5:234-54.
25. Paulson KG, Iyer JG, Tegeder AR, Thibodeau R, Schelter J, Koba S, *et al*. Transcriptome-wide studies of merkel cell carcinoma and validation of intratumoral CD8+lymphocyte invasion as an independent predictor of survival. J Clin Oncol 2011;12:1539-46.
26. Connelly T. Regarding complete spontaneous regression of Merkel cell carcinoma. Dermatol Surg 2009;35:721.
27. Eggers SD, Salomao DR, Dinapoli RP, Vernino S. Paraneoplastic and metastatic neurologic complications of Merkel cell carcinoma. Mayo Clin Proc 2001;76:327-30.
28. Cher LM, Hochberg FH, Teruya J, Nitschke M, Valenzuela RF, Schmahmann JD, *et al*. Therapy for paraneoplastic neurologic syndromes in six patients with protein A column immunoadsorption. Cancer 1995;75:1678-83.
29. Lopez MC, Pericay C, Agustí M, Martinez-Gallo M, Bordes R, Gelpí C. Merkel cell carcinoma associated with a paraneoplastic neurological syndrome. Histopathology 2004;44:628-9.
30. Greenlee JE, Steffens JD, Clawson SA, Hill K, Dalmau J. Anti-Hu antibodies in Merkel cell carcinoma. Ann Neurol 2002;52:111-5.
31. Assouline A, Tai P, Joseph K, Lian JD, Krzisch C, Yu E. Merkel cell carcinoma of skin-current controversies and recommendations. Rare Tumors 2011;3:e23.
32. Andea AA, Coit DG, Amin B, Busam KJ. Merkel cell carcinoma: Histologic features and prognosis. Cancer 2008;113:2549-58.
33. Wang TS, Byrne PJ, Jacobs LK, Taube JM. Merkel cell carcinoma: Update and review. Semin Cutan Med Surg 2011;30:48-56.

Cite this article as: Gaopande VL, Joshi AR, Khandeparkar SG, Deshmukh SD. Merkel cell carcinoma of the abdominal wall. Indian Dermatol Online J 2015;6:269-73.

Source of Support: Nil, **Conflict of Interest:** None declared.