

Metastatic basal cell carcinoma of the head and neck

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Five new cases of metastatic basal cell carcinoma are presented to highlight the potential of this tumor to develop malignant metastases. Histologic criteria of the primary and metastatic site are presented along with a review of the pertinent world literature. (OTOLARYNGOL HEAD NECK SURG 93:78, 1985.)

Basal cell carcinoma (BCC) is the most common cutaneous neoplasm, accounting for 75% of all skin cancers¹ and involving the head and neck region in 85% of the cases.² Spread by chronic local extension is the rule, but rare metastases do occur.

The first documented case of metastatic BCC was reported by Beadles³ in 1894. Since then approximately 110 cases^{4,41} true metastases, meeting the diagnostic criteria of Lattes and Kessler,⁴ have been reported. To qualify, these lesions must originate from the skin and not from mucous membranes or salivary gland tissue.

They must be truly metastatic and not simply direct extensions from the primary. Last, the primary and metastatic cancers must be histologically identical and devoid of any squamous component. Five new cases of metastatic basal cell carcinoma are presented to highlight the potential of this tumor to develop highly malignant metastases. Histologic criteria of the primary and metastatic site are presented along with a review of the literature.

CASE REPORTS

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Case 1. A 43-year-old white man presented in 1945 with a basal cell carcinoma of the right lateral upper lip, which was resected and primarily reconstructed with a local advancement flap. The significant past medical history revealed he had been treated for carcinoma with radium implants in the left leg in 1938. Local recurrence of the lip tumor in 1951 required repeat surgical excision. In May 1954 recurrent basal cell carcinoma required total excision of the right upper lip. The area was reconstructed with a transposed temple flap. In November 1961 a recurrent tumor was noted in the margin of the scalp flap with involvement of the right upper alveolus. The tumor was totally excised, and a lower lip flap was used for

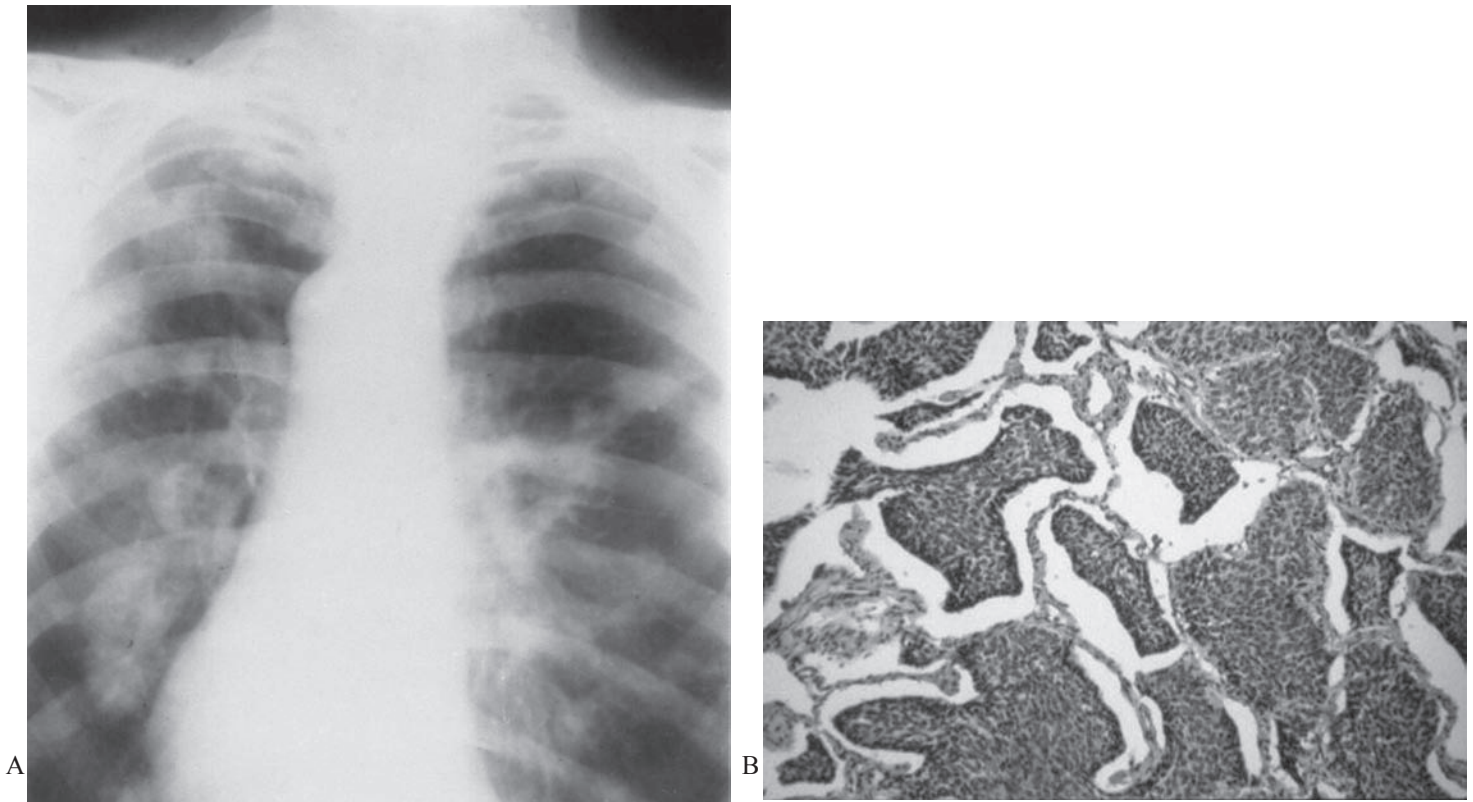


Fig. 1 A, Chest x-ray film showing diffuse metastatic basal cell carcinoma to both lung fields. **B**, Metastatic basal cell carcinoma to lungs showing classical histologic pattern and intra-alveolar spread. (Original magnification X160.)

reconstruction. In 1965 a mass in the right cheek was noted. This was biopsied, and recurrent tumor was found. Chest x-ray films taken at that time showed scattered 1 to 2 cm nodules throughout both lung fields. On October 1965 the patient underwent a left anterior lateral thoracotomy with an open lung biopsy. Pathologic diagnosis was metastatic basal cell carcinoma to the lungs. The patient continued to deteriorate with further local spread of the primary tumor. He died in 1973 from pulmonary failure secondary to extensive metastatic tumor spread (Fig. 1).

Case 2. A 56-year-old white woman presented in November 1946 with a recurrent basal cell carcinoma of the right eyebrow. A tumor had been surgically extirpated and primary repair had been performed at that site 2 years earlier. On November 30, 1946, a local elliptic excision was performed and repaired with a split-thickness skin graft. The pathologist commented at that time that the basal cell carcinoma was completely removed but the cells seemed "more atypical" than usual in this type of tumor. The patient remained free of disease until June 23, 1950, when a recurrent basal cell carcinoma was aggressively removed from the previous operative site; the resection included the supraorbital rim, periosteum, and eyebrow. Primary reconstruction was performed with a post auricular hair-bearing flap. Microscopic analysis revealed all margins to be free of basal cell carcinoma. On June 16, 1954 she presented with recurrent tumor of the right eyebrow, which was resected along with the surrounding periosteum and superficial cortex of the frontal bone. Repair with split-thickness skin graft was accomplished primarily. In 1958 and early 1961 there were local re-excisions of recurrent basal cell carcinoma in the same right forehead region. Multiple electrodesiccations were also performed during this time. On December 16, 1961, a 1 cm firm, fixed, right

intraparotid mass was identified. No forehead tumor was evident. On December 15, 1961, a right lateral parotid lobectomy revealed a metastatic basal cell carcinoma to an intraparotid lymph node (Fig. 2). Until the patient's death of unrelated causes on February 14, 1969, she required multiple excisions and electrodesiccations of recurrent basal cell carcinoma of the upper right face.

Case 3. This 50-year-old white woman presented in October 1966 with a 1 x 2 cm basal cell carcinoma of the right upper lip adjacent to the vermilion border. Recent symptoms included bleeding and scabbing. Her past medical history revealed two separate prior excisions of basal cell carcinoma in the same area in 1957 and 1963. Wide local resection was performed on October 15, 1966, and primary repair accomplished with a lip-cheek flap. Pathologic analysis revealed basal cell carcinoma with invasion of the underlying muscle. The patient remained asymptomatic until March 1975, when routine examination revealed a firm, right submental lymph node. Observation for 3 months showed no resolution of the mass. On June 6, 1975, an excisional biopsy of the node was performed, which revealed metastatic basal cell carcinoma to a right submental lymph node. On June 27, 1975, a wide excision of the right submental area with suprahyoid dissection was performed; all margins were free of tumor. The patient showed no evidence of recurrent disease when lost to follow up in November 1976 (Fig. 3).

Case 4. This 50-year-old white man presented with a history of basal cell carcinoma of the right medial canthus and forehead in 1969. In 1975 a second basal cell carcinoma was excised from the right upper cheek, which revealed atypical basaloid features on histologic examination. In May 1977 he presented with a 3-month

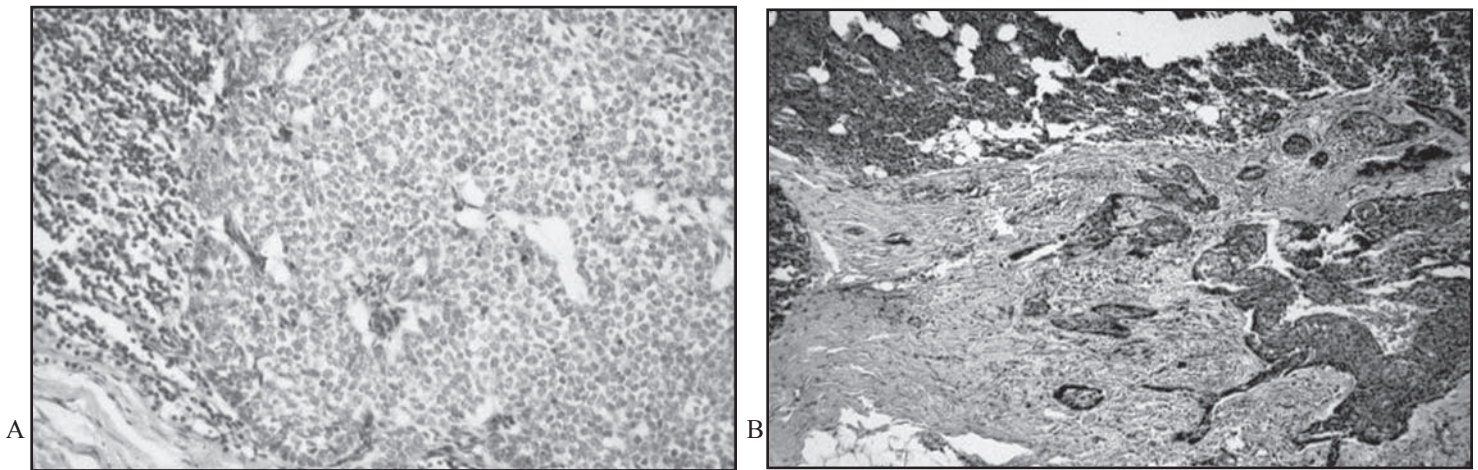


Fig 2. A, Intraparotid lymph node with metastatic basal cell carcinoma. Note typical palisade. Arrangement of peripheral cells at left hand corner. **B,** Direct extension of basal cell carcinoma into capsule and parenchyma of parotid gland. (**A,** original magnification x160; **B,** original magnification x100.)

history of progressive swelling in the right pretragal region, which was excised on May 6, 1977. Dr. R. Lattes reviewed all pathologic slides, and a diagnosis of metastatic basal cell carcinoma to a right periparotid lymph node was confirmed. On June 2, 1977, a total right parotidectomy with right upper neck dissection and facial nerve preservation was performed. No recurrent tumor or residual basal cell carcinoma were found. To date the patient has not shown any evidence of recurrent disease (Fig 4).

Case 5. A 69-year-old white woman presented in 1978 with chronic drainage from the right lateral canthal region with surrounding firm nodularity. The medical history revealed prior excision of a basal cell carcinoma from the right temple and lateral canthal region in 1971. Multiple surgical excisions for recurrent tumor had been performed over the intervening years. After positive biopsies for recurrent infiltrating basal cell carcinoma, the patient underwent right radical orbital exenteration, partial right maxillectomy, and primary reconstruction with forehead flap on May 11, 1978. The patient developed a parotid duct fistula in 1980, which was reconstructed with local mucosal flaps. In March 1981 she presented with recurrent basal cell carcinoma in the maxilla and palate, and on March 5, 1981, she underwent resection of the palate, maxilla, and cheek, with a split pectoralis myocutaneous flap being used for reconstruction. In January 1982 the patient presented to her local physician with a 1.5cm nodule under the right mandibular ramus. Open excisional biopsy revealed metastatic basal cell carcinoma of a pre facial arterial lymphnode (Fig. 5). Following this diagnosis she underwent wide excision of the skin and soft tissue of the right cheek and upper neck, with primary closure on April 12, 1982. The patient did well until July 1983, when she presented with palpable nodes at the angle of the right mandible. Needle aspiration at that time was positive for basal cell carcinoma. On August 23, 1983, she underwent a total right radical parotidectomy and upper neck dissection; primary closure was accomplished. Future treatment plans include radiation therapy.

DISCUSSION

Incidence. The incidence of basal cell carcinoma is difficult to determine because many cases escape routine indexing and the ones reported usually are statistically skewed. In 9050 cases at Memorial Hospital in New York, Cotran¹⁷ found only nine cases of metastasizing basal cell carcinoma, reflecting an incidence of 0.1% in a preselected referral population. Hughes³⁸ found two cases in a series of 499, and a New Zealand Australian survey reported a 0.0028% incidence in an area reputed to have the highest incidence of primary basal cell carcinoma in the world.⁴²

Age, race, and sex. The majority of metastasizing basal cell carcinomas occur in Caucasians between the ages of 20 to 60 years with a male predominance over women of 2.1:1. There have been only two cases of metastasis in black patients, but their primary tumors were not exclusively in the head and neck region.^{43,44}

Morphology - primary tumor. Primary neoplasms are generally large, ulcerating, locally invasive over a prolonged period, and refractory to surgical, electro desiccation, and irradiation therapy. Most patients have single primary tumors, but multiple sites have been reported.^{4,28} The majority of basal cell carcinomas are located on the face, especially in the middle third of the face. Predilection for the mid face may be the result of the greater exposure of this area to sunlight⁴⁵ and the fact that skin and subcutaneous tissue in the midface are relatively thin. Several studies have shown that basal cell carcinoma of the mid face has a higher recurrence rate than lesions of the upper or lower face.^{46,47} Histologic subtypes of basal cell carcinoma show that the solid type tends to be the least aggressive, whereas the morphea type and adenocystic type are much more aggressive and tend to infiltrate microscopically, both superficially and deeply, into surrounding tissue far from the primary site of origin.^{48,49}

Routes and mechanisms of metastasis. Eighty five percent of metastatic basal cell carcinomas occur from primary tumors situated in the head and neck region. Other less frequent primary sites include the back and the skin of the extremities.^{32,44} The most often cited metastatic route is through dissemination to regional nodal stations, which present in 60% to 70% of patients.^{25,40}

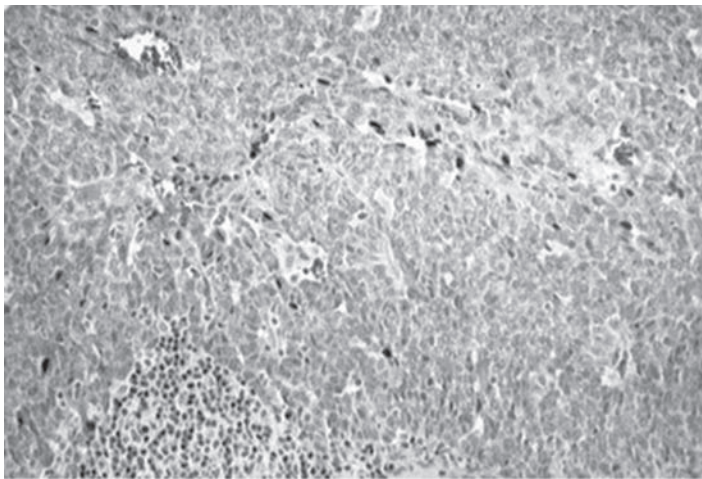


Fig. 3. Metastatic basal cell carcinoma of right submental lymph node. (Original magnification x160.)

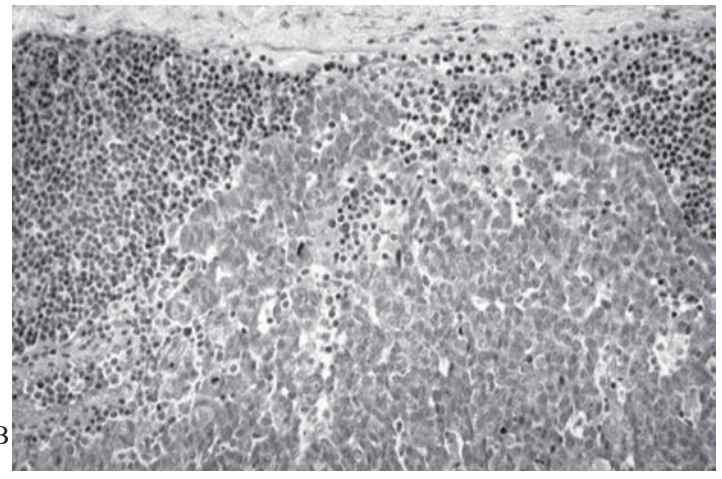


Fig. 4. Right peripartid lymph node showing metastatic basal cell carcinoma. Note palisading of nuclei of peripheral cells at top margin.

Hematogenous dispersion is the next most common route, and even direct implantation and proliferation in bronchi secondary to aspiration is known to occur.²⁷ Other representative sites of metastasis include lungs and pleura, 20% liver, 18%; bone, 17%; and, rarely, brain, spleen, pericardium, peritoneum, diaphragm, pancreas, and vena cava. Metastasis presents from 5 months to 45 years after primary diagnosis, with a mean of 11 years. Diagnosis is usually clinically evident, although occult metastases have been discovered at autopsy.¹⁷ It has been the goal of many investigators to identify a subclass of primary basal cell carcinoma that has a higher propensity for metastatic dissemination. Helwig and Thomas⁵⁰ describe a "metatypical" histologic pattern displaying large polygonal cells, with a tendency for peripheral palisading and increased cytoplasmic eosinophilia, which he thought indicated a higher probability of metastasis when present. Conway and Hugol indicated previous treatment by radiotherapy as a causative factor in metastasis, theorizing a radiation induced biologic transformation of the primary, thus characterizing a subgroup that may eventually metastasize. There is an initial nature to some of these primary tumors that has been accurately described as "horrifying," implying a super aggressive primary with an outstanding predilection for with standing multiple treatment modalities.³⁷ These primaries do tend to metastasize more often but the mechanism is disputed. Some believe that the primary tumor is de novo a more resilient species, and others imply multiple external stimuli from recurrent therapy as a causative factor. It should be noted, however, that many primary tumors do not have in a horrifying way and remain completely in dolent after routine therapy, only to metastasize many years later. More recently, several authors have reported that specific histologic findings in the primary tumor may delineate the more highly infiltrative, aggressive tumor. Batsakis⁵¹ states that the nucleus and the nucleolus are large and the chromosome pattern is coarse in these tumors, with foci of dystrophic calcification. The presence of irregularities in the peripheral palisading of basal cell carcinoma, the absence or minimal presence of lymphocytic infiltration, the presence of squamous differentiation,⁴³⁻⁵² and a high rate of mitotic activity "greater than 10 per 5 hpf"⁴³ have also been observed in the more aggressive tumors. Although the clinical presentation of a primary basal cell carcinoma that metastasizes is well characterized as being extensive, locally invasive, and chronically unresponsive to conventional therapy, there seems to

be no reliable set of factors that would accurately predict eventual biologic behavior of the tumor. The intrinsic cellular mechanisms that allow for metastasis are still obscure, but some facets of these relationships in basal cell carcinoma have come to light. In 1953 Pinkus⁵³ described the basal cell carcinoma as a neoplasm that required a connective tissue stroma to survive. Assor²³ subsequently theorized that the entire tumor unit, including the basal cell carcinoma of the stroma, must be totally detached from its surrounding tissue bed to metastasize. Van Scott and Reinertson⁵⁴ substantiated Assor's theory when they successfully autotransplanted basal cell carcinoma with its attendant stroma, but failed to do so when it was absent, implying a definite modulating influence of the stromal environment on the neoplastic epithelium.⁵⁵ It is theorized that the metatypical basal cell carcinoma has developed a stromal independence, thus allowing for autonomous migration.⁵⁴ The series of events leading to metastasis are complex, interrelated, and, for the most part, still quite obscure. The very fact that a long interval usually persists between diagnosis of the primary tumor and eventual metastasis implies a basically docile tumor that is influenced both by external agents, including therapeutic manipulation, and by the internal immunologic milieu of the host. Recently it has been suggested that the immuno compromised caecesthetic patient may be at more risk of metastatic spread of basal cell carcinoma,^{53,57} and that complete immunologic and nutritional assessment be obtained in these patients. Criteria for assessment of immunologic competence^{40,43,53} include (1) number of T and B cells, (2) level of serum-immunoglobulins, (3) leukocyte function, (4) skin testing with purified protein derivative, streptokinase, streptodornase, mumps, and dermatophytin, and (S) total lymphocyte count. Criteria for assessment of nutritional status⁽⁵⁷⁾ include (1) nitrogen balance, (2) midupper arm circumference measurement, (3) triceps skin fold test, (4) creatinine height index, (5) serumtransferrin albumin and total iron binding capacity (TIBC).

Prognosis. Despite vigorous therapy, the prognosis for a patient in whom metastasis has occurred is grave, with the mean survival time after identification of metastasis of 10 to 14 months.^{5,13} Although several reports indicate prolonged survival with metastasis to regional lymph nodes, only a handful of patients with distant metastases have survived more than 1 year. Death is usually associated with metabolic compromise rather than direct involvement of vital organs.^{41,43}

Treatment. At the time of metastatic diagnosis, most primary tu-

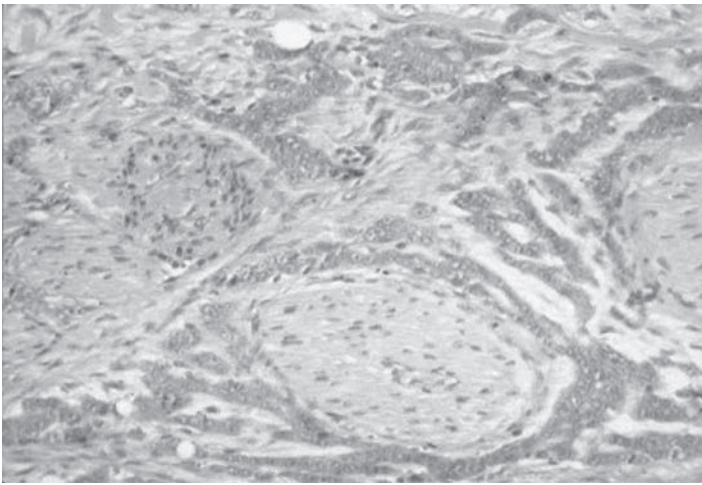


Fig. 5. Recurrent basal cell carcinoma in subcutaneous tissue with involvement of perineural spaces.

mors were present even after heroic attempts had been made over many years to eradicate them with repeated surgical procedures, irradiation, or electro desiccation. Initial radiotherapy was the primary treatment modality in many of the reported cases, although surgical excision was more common in our series. Two factors, however, argued against continuing radiation as a primary treatment. There is more than some speculation that radiation may induce meta static activity in the primary tumor, also, it is thought that the adequacy of the treatment is not easily documented after radiation, thus allowing for subsequent growth of neoplasm for long periods before detection. Chemotherapeutic agents such as cyclophosphamide, actinomycin, S-fluorouracil, and methotrexate have been used with very little success. Adjunctive agents such as methadone, prednisone, L-dopa, mithramycin, and parathormone have provided symptomatic relief and appear warranted when metabolic abnormalities compromise the patient. Adequate, complete excision of the primary tumor is the major objective, and because many basal cell carcinomas have subclinical micro extension into the surrounding normal tissue, simple elliptic excision of the tumor often results in residual tumor in the primary site. Routine surgical excision of the simple basal cell carcinoma may result in a relatively high cure rate, but when dealing with more diffuse or chronic basal cell carcinoma, cure rates in the range of 40% to 50% are obtained with curettage and desiccation, surgery, or irradiation. In similar tumors, Moh's surgical technique results in 95% or greater cure rates. This technique of excising all parallel sections of the resected tumor's borders results in an adequate removal of all microfoci, no matter which direction they are projecting. Therefore, we believe that Moh's surgical technique is the treatment of choice in accomplishing adequate surgical extirpation of the primary basal cell carcinoma. Mikhail et al^{9, 30} further conclude that the primary reconstruction should be delayed at least 6 months to verify completeness of the excision. If major reconstructive measures are utilized sooner, they believe that residual tumor may take the path of least resistance and infiltrate into deeper tissues before declaring itself on the surface. To date, all treatment modalities designed to eradicate the metastatic lesion have been uniformly disappointing. One metastatic pulmonary lesion was successfully resected, but there have been no other such reports of successful surgical control of distant metastases²⁴ Safai and Good⁴⁰ report eight cases in which aggressive chemotherapy

failed completely. This, however, may reflect the oncologist's lack of experience with this tumor and not a testament to the wild, aggressive nature of the neoplasm. Therefore, unfortunately, symptomatic and expected care is all that can be currently offered.

CONCLUSIONS

It is readily apparent that the rare metastatic event in basal cell carcinoma occurs only after inexorable existence as a primary lesion. In light of increasing evidence implicating the immune system as a primary factor in oncologic containment, it seems logical to assume that over a significant period of time, an interaction between the traumatizing effects of multiple therapies and the possible alterations in the host's immune organization, influenced by the overall physiologic status of the patient or some tumor specific agent, finally allows for a seemingly indolent primary lesion to attain stromal independence and metastasize. Thus, it behooves the astute clinician to subclassify those patients with chronic, locally aggressive basal cell neoplasms as potential risks for the development of metastases. The most expedient preventive measure is an initial, thorough, complete surgical extirpation of the primary. In addition, periodic bone, liver, and spleen scans, as well as chest x-ray films, alkaline phosphatase determinations, and a periodic search for regional lymphadenopathy would appear reasonable in selected cases.

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