Axillary Metastases from Unknown Primary Sites

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CANCER, first detected by biopsy of an axillary mass, can be a perplexing diagnostic problem. Often a good history and physical examination will reveal the site of the primary lesion. All too frequently, however, examination of the gastrointestinal and genitourinary tracts, skin, thyroid, lungs, breast, or head and neck, fails to reveal a primary malignant neoplasm. Feuerman, Attie, and Rosenblum[1] reported the cases of 21 such patients in 1962. One third of these patients proved to have mammary cancer. We were interested in the follow-up of patients without proven mammary cancer.

Review of the records of the past 20 years at The University of Texas at Houston M. D. Anderson Hospital and Tumor Institute revealed 60 patients with axillary metastasis and no known primary site on initial evaluation. Each patient's work-up included a thorough history and physical examination (specifically oriented to the detection of skin cancer), full radiographic and diagnostic genitourinary and gastrointestinal studies, bone survey, chest X-ray film, thyroid evaluation, mammography, brain and liver scans when available, and complete head and neck examination. Nineteen of these patients, approximately one third, were subsequently treated for mammary cancer, of whom 18 instances were proved antemortem and reported separately by Westbrook and Gallager.[3] The 42 remaining patients (Table 1) are reviewed in this report in an attempt to formulate a plan of treatment for patients with axillary metastasis from an unknown primary site and to predict the fate of these patients.

Clinical Material

Epidemiologic data were of minimal prognostic value. Figure 1 shows the age distribution when axillary malignancy was first discovered. The youngest patient was 5 years old; the oldest was 82. Sex distribution was relatively even, 23 males and 19 females. Thirty-six of the patients were white and six black. All six Negro patients were female.

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In 32 patients, a palpable mass was the only presenting symptom; it was usually discovered by the patient while bathing. In ten of the patients, both mass and pain were the presenting symptoms. The size of the lesion when the patient was first seen was variable, ranging from 1.5 cm. to 9 cm. in diameter. As for tumor site, 20 were initially noted in the right axilla and 22 in the left. Medical advice was usually sought between 8 and 24 weeks after initial detection of the mass; the range, however, was from 1 week to 1 year. In only three of the 42 patients was the organ of primary origin discovered antemortem. Thus the majority of these patients were followed throughout their life span without definite determination of the primary site.

Non-survivors in Whom Site of Origin was Undetermined

Twenty-four patients, in whom a definitive primary lesion was never found, died of the disease (Table 1). When initially evaluated, 12 of these patients had no evidence of metastasis other than in the axilla. The remaining 12 patients had other metastatic sites on first evaluation. Patients who initially had detectable metastasis in the axilla only survived a longer period of time. Their mean survival was 21 months as compared to 11 months for those with other metastatic foci. This difference did not appear to be a result of the latter group's reluctance to seek medical advice. The mean interval between onset of disease and treatment in the group with no other metastasis was 2.4 months as compared to 4 months for those with metastasis.

Eight of the 12 patients without other metastatic sites had axillary dissection following thorough evaluation. Positive nodes were identified in each case. In five patients more than one half of the recovered nodes contained tumor. In each instance, axillary dissection was performed for patients with unclassified malignancy but

TABLE 1. *Outcome of 60 Patients Initially Presenting with Axillary Metastasis from an Unknown Primary*

Diagnosed and treated as primary breast cancer		18
Dead with site of origin undetermined	24	
Dead with site of origin determined	9	
Survived with no evidence of disease	9	
	42	
Total		60

TABLE 2. *Sites of Nonaxillary Metastasis*

Site	Nonaxillary Metastasis Detected at Initial Evaluation	Nonaxillary Metastasis Detected Subsequent to Initial Evaluation
Supraclavicular (ipsilateral)	3	3
Lung	7	5
Generalized dermal	1	4
Recurrent axillae	0	2
Brain	1	0

with elements suggestive of squamous cell carcinoma or amelanotic melanoma. Those patients with other metastatic foci had multiple forms of palliative therapy, including chemotherapy and radiotherapy. No definite evidence of disease regression could be identified.

In those 12 patients without evidence of disease outside the axilla, further metastasis occurred on an average within 14.5 months. After the axilla, the supraclavicular nodes were the next site of lymphatic drainage, but were not necessarily the next site of disease spread. The lung or dermal metastases were more likely sites (Table 2). Similarly, the site of further metastasis on initial evaluation at MDAH was the pulmonary parenchyma (Table 2).

Non-survivors in Whom Site of Origin was Determined

Nine patients had definitive primary diagnoses either from axillary biopsy or at postmortem (Tables 1 and 3). All nine are dead from the disease. Three of the patients were male, six female. The average age was 54 with a range between 43 and 72. In six of these patients the primary lesion was not found until postmortem examination. Local excision was the usual mode of surgical therapy and metastatic deposits other than in the axilla were rapidly discovered. In the patient with Hodgkin's disease, the breast was believed to be the primary site and was treated with comprehensive radiation. At postmortem, Hodgkin's disease was discovered. Three patients had mucin-producing adenocarcinomas, diagnosed on axillary biopsy, two of whom have subsequently died. At postmortem these two patients were found to have had primary stomach cancer which had not been obvious on clinical evaluation. The third patient underwent local axillary excision in 1967, which revealed mucin-producing adenocarcinoma. This evaluation and one in 1969 failed to reveal a primary site. The patient was given prophylactic 5-fluorouracil in 1969 and remained free of disease, although he is still on medication at last evaluation (Table 4).

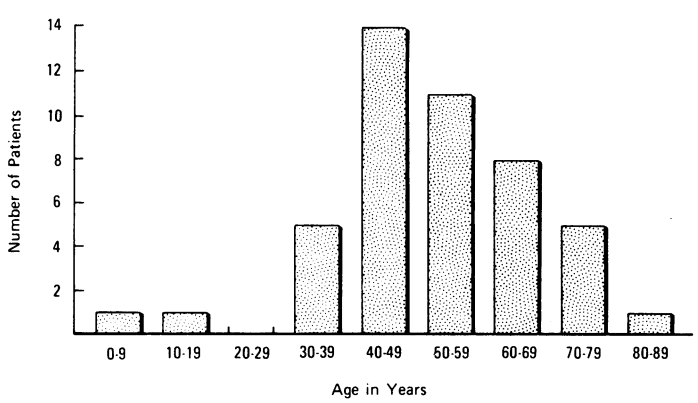

FIGURE 1

Patients Surviving with No Evidence of Disease

Nine patients remained free of disease 2 to 10 years after initial diagnosis of a malignant lesion in the axilla (Tables 1 and 4). Two of these patients died of other causes 2 years after the initial discovery of the disease, and no evidence of residual malignancy was found at postmortem examination. In no instance was the primary origin of the malignancy located. Five of the patients were male, four female; seven were white and two black. The average age of the patients was 54, with a range between 43 and 72 years. The distribution of these figures is similar to that for the whole series. In two of these patients, axillary dissection was carried out because there was a suggestion of amelanotic melanoma. There was one positive node in one patient; none in the other. The other seven patients had local excision as the only form of surgical therapy.

TABLE 3. *Summary of Patients with a Definitive Pathologic Diagnosis*

Diagnosis (One patient each)	Length of Life Following Axillary Diagnosis (months)	Mode of Surgical Therapy
Lung (Postmortem)	36	Axillary dissection (16/19 positive nodes)
Breast (Postmortem)	24	Local excision
Rhabdomyosarcoma	12	Local excision
Fibrosarcoma	8	Local excision
Stomach (Postmortem)	8	Local excision
Neurogenic sarcoma	6	Axillary dissection (12/18 positive nodes)
Stomach (Postmortem)	6	Local excision
Hodgkin's (Postmortem)	6	Local excision
Pharynx (Postmortem)	6	Local excision

Three of the surviving patients had undifferentiated metastases possibly from a primary lesion in the breast. Each patient received comprehensive radiotherapy and was free of disease 2 to 5 years post-therapy.

Table 5 lists the pathologic diagnoses of the axillary specimens removed from these nine patients as well as the 24 patients who died with no known primary site. The accuracy of the diagnosis of amelanotic melanoma or squamous cell components depended on the ability of the pathologist and more recently the use of electron microscopy. Nevertheless, the present survival for each group based on pathologic diagnosis was consistently 20 to 30 per cent (Table 5) with the exception of those with mucin-producing metastatic lesions. Those patients with a squamous element survived longer after diagnosis of the disease than did those in the other two groups.

TABLE 5. *Pathological Diagnosis of Axillary Mass in Patients with Primary Site Undetermined to Date*

	Total	Survivors (No Evidence of Disease)	Average Survival (Dead with Disease)
Poorly differentiated (Unclassified)	15	4	15.5 months
Poorly differentiated (Possibly amelanotic melanoma)	10	2	10 months
Poorly differentiated (Suggest squamous ca.)	7	2	30 months
Poorly differentiated (Mucin producing)	1	1	0 months

Conclusion

The physician must formulate an approach to treatment of axillary metastasis from an unknown primary site. Obviously all diagnostic methods to determine a primary source must be used. A thorough search of the skin of the extremity and trunk draining the ipsilateral axilla must be made. The possibility of a "disappearing" primary melanoma[2] or a small squamous cell lesion must be kept in mind. The patient should be questioned about previous skin lesions removed by electrocautery. Special staining technic and electron microscopy can be a great aid to the pathologist in diagnosing melanoma and various types of sarcomas.

In the experience of Feuerman, Attie, and Rosenberg,[1] once malignancy reached the axilla from an extramammary site, there were unequivocal signs pointing to the diseased organ of origin. This was true in very few of our patients. Nevertheless, we would agree with these authors and with Westbrook[3] that the breast is the most likely source of an undifferentiated axillary malignant lesion in women. In women with unclassified malignancies in whom no evidence of an extramammary source can be demonstrated, comprehensive radiotherapy to the ipsilateral breast and peripheral lymphatics would seem to be the treatment of choice. In those women with pendulous breasts or gross disease remaining in the axilla, a simple or extended simple mastectomy should be performed in order to make delivery of radiotherapy more efficacious. In women with small or atrophic breasts and minimal axillary disease, particularly those patients in whom no evidence of a breast primary can be demonstrated by mammography, xerography, or thermography, a mastectomy prior to radiation is not recommended. Radical mastectomies should not prove necessary.

Those patients with melanoma localized within the axillary lymph nodes should have an axillary dissection. The number of involved nodes can probably be used as a prognostic guide. Certainly those with more than five nodes involved have a poor prognosis. Men with unclassified malignancies should have axillary dissections for local control and, hopefully, for disease eradication. This also holds true for sarcomas localized within the axillary contents. Most patients with squamous cell lesions in this series were treated with local excision; squamous cell cancers tended to metastasize widely before recurring in the axilla. Experience with squamous cell metastasis to the axilla from known primaries, however, leads us to recommend axillary dissection for those with unknown primaries as well. These metastases if left alone, tend to become bulky and ulcerate, often requiring forequarter amputation for palliation alone. Needless to say, the patients require close follow-up study and proper therapy for the primary or metastatic disease as it becomes clinically apparent.

TABLE 4. *Summary of Patients Free of Disease on Last Follow-up Evaluation*

Pathologic Diagnosis	Length of Life Following Diagnosis	Primary Mode of Therapy
Undifferentiated Suggest squamous ca.	10 yrs.	Local excision
Undifferentiated Suggest squamous ca.	8 yrs.	Local excision
Unclassified	5 yrs.	Local excision
Mucin producing adenocarcinoma	5 yrs.	5-FU
Unclassified	5 yrs.	Comprehensive XRT
Unclassified	2 yrs. (Dead, no evidence of malignancy)	Comprehensive XRT
Unclassified	2 yrs. (Dead, no evidence of malignancy)	Comprehensive XRT
Unclassified	2 yrs.	Axillary dissection (0/18 positive nodes)
Undifferentiated Suggest melanoma	2 yrs.	Axillary dissection (1/25 positive nodes)

References

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