Reminder of important clinical lesson

FNA diagnosis of malignant melanoma-recurrent and metastatic disease

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Summary

We present a case of a 60-year-old woman with multiple right axillary swellings. Patient had a history of lump with pigmentation over back for which she was operated upon. There was also a nodule over resected scar on back. A final diagnosis of malignant melanoma (recurrent and metastatic to axillary lymph nodes) was rendered with the help of fine-needle aspiration cytology (FNAC). Malignant melanomas are the most lethal of cancers of the skin and are notorious for the great variability of cytological presentation. We discuss the role of FNAC in early diagnosis and prognostication of recurrent and metastatic disease.

BACKGROUND

Melanoma is an aggressive malignancy with a growing prevalence. Recurrences and metastases are not uncommon. Fine-needle aspiration (FNA) can play a vital role in their detection as a relatively non-invasive, rapid and economical alternative for tracking disease evolution. Prior clinical history and classic cytological features of melanoma aid in cytological diagnoses. However, not all melanomas contain melanin pigment or characteristic cytological features and therefore pose diagnostic dilemma.¹

CASE PRESENTATION

A 60-year-old woman with multiple axillary swellings presented in surgery out-patient department and was referred to cytopathology for FNA cytology (FNAC). The patient had a history of a pigmented nodule over back (right side) for which she was operated upon few years back, at some other centre, and had only few records available with her. According to the past records, the nodule was 6 mm in size, and was clinically considered benign; however, after an excisional biopsy with adequate margin, a malignant melanoma measuring 2 mm in primary tumour thickness was diagnosed. There was no axillary lymphadenopathy at that time, so no nodal dissection was done, and patient was asked to follow-up regularly. But the patient did not follow-up and after 2 years, now has presented with the current complaints.

On examination multiple (3 in number) swellings in right axilla along with a nodule m/s 1 cm in diameter over the resected scar on back (right side) was noted. FNA smears were prepared from both sites with 22-gauge needle and stained with H&E and PAP.

On microscopy of the smears prepared from nodule on back, classic cytological features of melanoma: highly cellular loosely cohesive smear pattern (figure 1) with round to polygonal cells (few spindle cells) having moderate cytoplasm, large nuclei (often eccentric), prominent nucleoli and vacuole and occasional binucleate forms were seen

(figure 2). Intracytoplasmic brown melanin pigment was also noted (figure 3). Smears from the axillary lymph nodes showed similar cytomorphology (figures 4 and 5). A final diagnosis of malignant melanoma (recurrent and metastatic to axillary lymph nodes) was rendered.

A whole-body CT scan was advised, which did not show any evidence of distant metastasis. Serum lactate dehydrogenase levels were normal. Due to the poor general condition and severe anaemia, surgery was postponed and she was advised haematinics and nutritious diet. Patient was started on combination chemotherapy (CVD regimen) with radiotherapy. On a follow-up chest x-ray after 4 months, presence of distant lung metastasis was documented which was also confirmed by a CT scan.

The patient was explained the prognosis, and was advised close follow-up; but she died within 3 months.

DISCUSSION

Melanoma is defined as a potentially lethal melanocytic neoplasm involving the dermis and the epidermis or

Figure 1 H&E-stained fine-needle aspiration cytology smear showing the cellular loosely cohesive smear pattern (×10).

Figure 2 Smear showing the round to polygonal cells with large nuclei (often eccentric), prominent nucleoli, occasional binucleate forms and focal intracytoplasmic brown melanin pigment.

dermis alone. Malignant melanomas are the most lethal cancers of the skin that occur mainly in fair-skinned people in areas exposed to sun.² Most melanomas develop from melanocytes in the lower layers of the epidermis, sometimes in association with pre-existing pigmented nevi but more commonly as a spontaneous event. The melanocytic cells at the epidermis–dermis junction are transformed and become ballooned and acquire nuclear abnormalities in the form of enlargement and prominent nucleoli. Most, but not all, of these tumours are pigment-producing.

As, lymphnode metastasis (N) is one of the most important predictors of survival in malignant melanoma, the correct identification of melanoma cells in regional lymph nodes is important for clinical management. Immunostaining and electron microscopy are confirmatory tools in difficult cases.^{3 4}

Nearly all of the aspiration biopsy data reported in the recent literature pertain to metastatic melanoma,⁵ and distinguishing primary from metastatic melanoma is not possible in the aspirated sample.⁶

Malignant melanoma is notorious for the great variability of its cytological presentation and may mimic almost

Figure 3 Smear showing the melanin pigment in a binucleate tumour cell.

Figure 4 Smears from axillary lymph node also show similar cytological features, though melanin pigment was not clearly appreciated.

any malignant tumour. The principal cytological feature of malignant melanoma is the presence of cancer cells of variable sizes and configuration, provided with large nuclei, prominent, often multiple large, irregularly shaped nucleoli and large intranuclear cytoplasmic inclusions. Multinucleated giant cells, elongated spindly cells and cells with vacuolated cytoplasm may be observed.^{7 8} The common denominator of most tumours is the presence of melanin pigment in tumour cells. The pigment may be dispersed and finely or coarsely granular, obscuring other features of the cells. The diagnosis must be based on malignant features of the cells because the presence of pigment alone may be misleading. The chief culprit here is the melanin pigment phagocytised by macrophages, as this may occur in a variety of skin disorders. Basal cell carcinomas and other lesions (melanocytic carcinoid, melanotic schwannoma and melanotic paraganglioma) may occasionally shed pigment-containing cancer cells.^{8 9}

It can be difficult to distinguish melanin pigment from lipofuscin and hemosiderin in routine stained smears, and special stains (formalin-induced fluorescence, Masson-Fontana) may be required. A fine dust-like intracytoplasmic pigment in tumour cells is characteristic of

Figure 5 Smears from axillary lymph node also show similar cytological features, though melanin pigment was not clearly appreciated.

melanoma.¹⁰ The most prominent vacuolisation of the cytoplasm occurs in the so-called balloon cell melanoma and such cells may be mistaken for cells of metastatic adenocarcinomas.^{11–12} In a small percentage of cases, cells with rhabdoid features may occur. These cells are large, have large peripheral nuclei, large nucleoli and eosinophilic cytoplasmic inclusions, best seen in Papanicolaou stain.¹³ As is so common with other tumours, nuclear grooves may also be observed in cells of malignant melanoma.¹⁴

Melanoma has a varied differential diagnosis consisting of a variety of carcinomas, sarcomas and haematolymphoid malignancies that often comprise also of non-Hodgkin's lymphoma¹⁵ and plasmacytoma/myeloma.⁹ Confirmation requires immunohistochemical help.^{3–4}

The cytomorphological features of great assistance in the accurate cytodiagnosis of amelanotic melanoma are a high cell yield; dispersed pleomorphic cell population; inclusion-like prominent nucleoli and the presence of intranuclear cytoplasmic inclusions.⁹

In pleural fluid the diagnosis of metastatic melanoma is easy in cases of pigmented melanoma. An unequivocal diagnosis of metastatic melanoma by FNAC smears alone is however difficult without pigment in tumour cells. In Perry's series of 120 cases of melanomas, 60% were amelanotic in FNB samples.¹⁶

Although controversial and without prolonged survival, sentinel lymphnode biopsy (SLNB) is often performed, especially for T1b/T2+ tumours, mucosal tumours, ocular melanoma and tumours of the limbs. More recently, lymph node ultrasound (US) with FNAC is considered a potential cost-effective alternative for an SLNB.^{17–18} According to studies done by Voit *et al*,¹⁷ combined US and FNAC provides important information prior to SLNB in that both procedures identify metastases in the lymph nodes (sensitivity >80%). Although, rare studies have reported very low sensitivity which is attributed to tiny and necrotic lesions,^{19–20} most authors have emphasised the importance of USG-guided FNAC in the detection of sentinel lymph node metastasis.^{17–19–21} With a positive cytology of the sentinel node, surgeons can proceed with the direct radical lymph node dissection in patients with melanoma; thereby preventing unnecessary anaesthesia and surgical management as well reduce costs.¹⁷ Significantly, attempts have also been made to apply molecular-based techniques on the material obtained by FNA, as well as on exfoliative samples.^{22–26}

The prognosis of melanoma varies with the site and stage of the disease.^{27–28} Advanced disease with local recurrence, or distant metastasis carries a grave prognosis.²⁹

Fewer than 20% of patients with recurrent disease exhibit distant metastases especially to CNS, lung, gut and liver even without any intermediate lesion, sometimes many years after removal of primary tumour. In the remaining 80%, metastases are located at regular lymph node basins or corresponding in-transit distances. The 5-year survival rate for patients with regional lymph node metastases (American Joint Committee on Cancer Stage III) ranges from 13% to 45% depending on the number of the metastatic lymph nodes. Tumour follow-up schedules are geared towards the earliest detection of such recurrent disease to initiate appropriate treatment as soon as possible. The detection of lymph node metastases as early as possible thus is of great importance and can affect prognosis.³⁰

CONCLUSION

Melanoma has always been known to be a great mimic. Pathologists coming across pleomorphic primary or metastatic disease with features of squamous cell carcinoma or other tumours some of which may have pigment should always consider melanoma in their differential diagnosis, because eyes do not see what mind does not know. Any intracellular pigment containing malignancy should have high index of suspicion for melanoma.

Learning points

- Malignant melanomas are the most lethal cancers of the skin.
- Most, but not all, of these tumours are pigment-producing.
- Fine-needle aspiration cytology can play a vital role in their detection as a relatively non-invasive, rapid and economical alternative for tracking disease evolution.
- Cytologically malignant melanoma can have varied picture and has a long list of differential diagnoses.
- Correct identification of melanoma in regional lymph nodes is important for clinical management.
- Documentation of a new metastasis has a role in staging of melanoma.

Competing interests None.

Patient consent Obtained.

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