Rare disease

Stage IV malignant melanoma of unknown primary site in a young man

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Summary

Metastatic melanoma of unknown primary is a rare entity with low life expectancy. Inoperable metastatic malignant melanoma in lungs has a survival rate of <6%. Regression of the primary lesion is a well-documented theory in the literature, since melanoma is one of the tumours that can undergo regression. We present a case of a young man with metastatic malignant melanoma in lungs, whose survival duration is longer than expected even without metastasectomy.

BACKGROUND

The interesting thing about our case and the cause of our decision to write it up was 2-fold (1) we had to deal with a metastatic malignant melanoma of unknown primary which is a rare clinical entity and (2) the clinical course of our patient developed surprisingly well, since he remains alive and without signs of recurrence 4 years after the initial diagnosis.

CASE PRESENTATION

A 34-year-old man presented with a left-sided cervical mass, which was incidentally palpated a month earlier. The mass was located in the left posterior triangle of the neck; it was mobile, painless and firm to feel with no pathological skin changes or ulceration. Ultrasound examination of the neck revealed a two-lymph node complex. The largest node had a diameter of 2.1 cm and the smaller one had a diameter of 1.1 cm (figure 1). An excision biopsy of the lesion was performed. The lesion was hard, firmly attached to the adjacent tissues with no signs of inflammation.

Histopathology analysis revealed a mass of 3.7 cm diameter, which consisted of four lymph nodes. The largest one had a complete effacement of the lymph nodal architecture by a tumour process with epithelioid cells. Immunohistochemical analysis was performed and the neoplasm cells were found to be positive for Melan-A antigen, protein S-100 and HMB-45 antigen (figure 2A–C). The tumour cells were found to be negative for CD-34 antigen, epithelial membrane antigen and inhibin. On the basis of these findings the diagnosis of melanoma was set.

The patient underwent a thorough examination that included the entire skin surface and all mucosal surfaces, ear, nose and throat (ENT) examination, ophthalmological examination, upper and lower gastrointestinal (GI) endoscopic examination, CT scan of thorax, abdomen and pelvis, MRI of the brain, as well as position emission tomography (PET) scan. Biochemical markers specific for the melanoma such as LDH and alkaline phosphatase (ALP) levels were unremarkable. The Wood's UV lump failed to

reveal areas of depigmentation of the skin or halo nevus or scars of regressed melanoma. CT scan showed and PET scan confirmed the presence of a suspicious lesion in the lower lobe of the left lung (figure 3) and the diagnosis of a secondary metastasis of unknown primary origin was suspected. A detailed medical history was taken, while the patient could not recall a prior skin lesion that could be characterised as the primary melanoma site.

The oncological board advised metastasectomy but the patient did not give consent. Chemotherapy administration was eventually decided. The patient received eight cycles of combined chemotherapy including dacarbazine and sorafenimib. The first cycle was administered 4 weeks after the excision biopsy. Since then, the patient proceeds for follow-ups every 6 months. Three years after the diagnosis of melanoma of unknown primary (MUP) site, the follow-up CT examination revealed multiple metastatic

Figure 1 Pre-excision ultrasound exam of the left posterior triangle of neck showing the lymph node complex.

(a)

(b)

(c)

Figure 2 (A) Lymph node infiltration by large epithelial cells with melanocytic characteristics. (B) Melanocytic cells positive for S-100 antibody. (C) Melanocytic cells positive for HMB-45 antibody.

nodules (figure 4A). Following that, eight more cycles of chemotherapy based on paclitaxel were administered. After the completion of the last chemotherapeutic cycle, CT scan of chest, abdomen and pelvis, revealed neither pathological mediastinal lymph nodes, nor pathological findings or metastatic disease in the abdomen, when compared with the previous CT scan. Moreover, there has

Figure 3 Position emission tomography/CT images showing the suspicious metastatic lesion in the lower lobe of the left lung.

been a transformation of the metastatic lesions in the lung parenchyma from solid-type lesions to 'blurred glass' metastatic lesions (figure 4B).

(a)

(b)

Figure 4 (A) Multiple lung metastatic lesions prior to the second chemotherapy scheme. (B) Thorax CT, after the second chemotherapy scheme, that shows 'blurred glass' metastatic lesions, revealing the regression of the disease.

INVESTIGATIONS

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The patient underwent a thorough examination that included the entire skin surface and all mucosal surfaces, ENT examination, ophthalmological examination, upper and lower GI endoscopic examination, CT scan of thorax, abdomen and pelvis, MRI of the brain, as well as PET scan. Biochemical markers specific for the melanoma such as LDH and ALP levels were unremarkable. The Wood's UV lamp failed to reveal areas of depigmentation of the skin or halo nevi or scars of regressed melanoma. CT scan showed and PET scan confirmed the presence of a suspicious lesion in the lower lobe of the left lung and the diagnosis of a secondary metastasis of unknown primary origin was suspected. A detailed medical history was taken, while the patient could not recall a prior skin lesion that could be characterised as the primary melanoma site.

DIFFERENTIAL DIAGNOSIS

The result of the excision biopsy was typical for malignant melanoma.

TREATMENT

Our patient underwent excision biopsy of the lesion and this was followed by several chemotherapy cycles, since the patient did not consent to have a metastasectomy.

OUTCOME AND FOLLOW-UP

Our patient almost 4 years after the primary diagnosis is still alive with no signs of metastasis. His disease seems to be controlled. This is quite rare since patients with stage IV disease with no metastasectomy do not survive for that long period of time.

DISCUSSION

The metastatic melanoma disease that is diagnosed without identifying the primary lesion is known as MUP site. Das Gupta, in 1963, was the first to describe the exclusion criteria of a true MUP; history of orbital enucleation or exenteration, history of skin lesion removed, the presence of scar of previous local treatment in skin area drained by involved lymphatic basin, lack of thorough physical examination, including ophthalmic, anal and genital.^{1–4} Current literature has shown that the MUP concerns ~2–9% of all melanoma cases.¹ Savoia *et al*,⁵ in a series of 93 MUP patients, report that the lymph node involvement as the first manifestation of the disease occurred in half of the examined cases. The theories concerning the aetiology of MUP are: (1) spontaneous regression of the primary lesion, (2) unidentified primary melanoma, (3) previous excision of what was initially

considered a benign lesion and (4) a primary origin of melanoma in lymph nodes.^{5–7} According to the reviewed literature, the most accepted theories concerning MUP presentation are the spontaneous regression and the infiltration of melanocytes in the lymph nodes.³ Melanoma is one of the three tumours that can undergo the regression status.⁴ The complete regression of cutaneous melanoma ranges from 3.7% to 8.7%.⁴ According to the literature, regression of a melanoma is more common in men who usually underestimate a dermatological lesion till it regresses and presents later as metastatic disease. Taking into consideration the location of metastatic lesions we have many reasons to believe that the primary lesion initially presented in the head or neck region. Our suspicion strongly agrees with the criteria for diagnosis of MUP which has completely regressed as they were set by Smith and Stehlin.⁴ The clinical and tests that have been proposed for setting the diagnosis of a primary melanoma include;⁸ detailed skin and sublingual examination, ophthalmological examination when metastases in the liver and lymph nodes are detected, ENT examination in cases of neck, oral or axillary metastases. When inguinal lymph nodes are found infiltrated then gynaecological examination must take place in females, whereas genitalia and penis should be examined in males. Finally, in both sexes, urinary bladder (cystoscopy) and anal (finger examination and proctoscopy) examinations must take place. The radiological investigations include full-body imaging with either CT or PET scan. The value of PET scan is limited in the detection of the primary lesion, but when it is combined with CT scan it becomes a very useful diagnostic tool in the staging of MUP and identification of stage IV disease.^{4–8} Tos *et al*,² in a retrospective study that included 103 MUP patients recommended that special clinical examinations should be redundant and the primary screening tests should be limited to a detailed history, a standard clinical examination in combination with histopathological review and CT/PET analysis.² The above consideration has also been confirmed in our case where the initial detailed physical and radiological tests were not diagnostic for the primary tumour apart from a suspicious lesion in the left lower lung (PET/CT finding) that was considered as a secondary metastasis. According to the revised AJCC 2009 melanoma staging system, lymph node metastases are classified as regional (stage III), and all other metastases are considered as distant (stage IV). The melanoma metastatic sites can be subdivided into three specific categories. M1a involves skin, subcutaneous or nodal metastases with normal LDH marker, M1b involves lung metastases with normal LDH marker and M1c is presented with any distant metastases with either normal or an elevated LDH marker. Our patient's status belongs to the M1b subcategory—metastatic lesion in the lung and normal LDH. The overall survival rates in patients with stage IV metastatic melanoma of unknown primary have reported similar to those of known primary site and there are estimate to be <8 months.^{6–9} The National Comprehensive Cancer Network recommend that metastasectomy in stage IV malignant melanoma should be performed when the metastatic disease is limited in one or only few sites, while adjuvant systemic therapy should follow. Our patient did not undergo surgical removal of the metastatic lung lesion even though he

met some of the suggested recommendations/criteria for the surgical removal of the metastatic lesions in the lung which were introduced by Oriaro *et al.*¹⁰ According to the literature,^{6 10} the 3-year survival rate postmetastasectomy in patients with stage IV malignant melanoma reaches 37%, whereas in patients who are treated with immunotherapy, chemotherapy and/or radiotherapy the survival rate is only 7%. Several studies have reported a 14–28% 5-year survival rate, in patients with stage IV melanoma postmetastasectomy.⁶ The critical point in our case is that our patient almost 4 years after diagnosis of metastatic melanoma and having only received chemotherapy treatment and no lung metastasectomy, has overcome the expected, according to the reviewed literature, survival rate and his disease seems to be controlled.

According to the known literature, there are quite a few cases with stage IV malignant melanoma, that have survived for so long having received only chemotherapy treatment and no metastasectomy. Wasif *et al*⁶ refer that patients with stage IV malignant melanoma with no metastasectomy have a median survival of 7 months and patients who undergo metastasectomy have much better survival rates. According to the same author, the 5 years overall survival in patients with no metastasectomy is only about 9%.

Learning points

- ▶ Malignant melanoma may present to a stage IV disease without identification of the primary site.
- ▶ The clinical course may be surprisingly better than expected.
- ▶ Long-term chemotherapy courses with no metastasectomy could also improve the survival and more studies should be done in this direction.

Competing interests None.

Patient consent Obtained.

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