ACHROMATIC METASTATIC MELANOMA ASSOCIATED WITH VON RECKLINGHAUSEN'S DISEASE – CASE REPORT

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Abstract: *Achromatic melanoma is difficult to diagnose clinically because the tumour is not pigmentary or is hypochromic and often poses differential diagnosis problems, requiring immunohistochemical investigations for confirmation. Diagnosis of cutaneous metastatic melanoma with direct identification of metastases is even more difficult in the absence of primary tumour. Neurofibromatosis type 1 (NF1), also called von Recklinghausen's disease is one of the most common genetic diseases. The disease is characterized by pigmented skin macules, (café-au-lait spots), neurofibromas, soft fibroids and Lisch nodules. It is caused by the NF1 gene mutation whose function is to inactivate the oncogene RAS gene, which allows tumours to develop. This is a case of association between type 1 neurofibromatosis (NF1) and metastatic achromatic MM, this association being rarely published in the literature. The specificity of the case consists of the diagnostic difficulty of an achromatic metastatic MM without identifying the primary tumour and the association with NF1; therapeutic options are also discussed in metastatic melanoma, taking into account the suprainfection associated with melanoma cutaneous metastases.*

INTRODUCTION

MM can be directly diagnosed as metastatic melanoma in 10-60% of cases.(1) There are situations when melanoma metastases confirm the disease, with or without subsequent identification of the original melanoma, which makes the diagnosis late and complicated. More difficult is when metastatic tumour lesions are achromatic, cannot meet dermatoscopic and histopathologic criteria and may require differential diagnosis between melanoma, sarcoma, squamous cell carcinoma (CSC) etc., requiring special IHC stains.

Neurofibromatosis is an autosomal dominant disease with high clinical variability. Four forms of NF have been distinguished (Riccardi, 1982), the first form is the most common, called von Recklinghausen's disease. Only half of the cases are inherited, the others are the result of new mutations.

Neurofibromatosis is the result of the effects that the abnormal gene has on elements derived from the neural crest: melanocytes, Schwann cells, fibroblasts at endonerve level.(2) Melanocytes produce the most common lesions in the von Recklinghausen's disease, namely café-au-lait spots. Patients with neurofibromatosis have a higher melanocyte count and normal pigmented skin too, than those who do not have the disease.(3) Also, these melanocytes also contain an increased amount of melanin. There are hypotheses that the disease is a pathology derived from the neural crest, melanocytes being also derived from the neural crest (4), produce the most common and constant elements in NF1, namely the café-au-lait spots. The association between NF1 and various malignancies has been reported in literature, (4,5,6,7) especially cerebral tumours and less frequently, medulloblastoma, pheochromocytoma, thyroid gland carcinoma and malignant tumours of the peripheral nerve sheaths. MM may also be associated with hemopathy.(8) Several associations between melanoma and von Recklinghausen's disease (4,7,9) have been reported.

CASE REPORT

A 68-year-old patient with no previous clinical evidence admitted to the Dermatology Clinic in Sibiu, presenting on the anterior face of the right calf five tumour infiltrated formations, the first one having occurred for about a year, with a large base of implantation, having a diameter of one to four centimetres, some of them having an ulcerated surface, covered by fibrinopurulent secretions.

The general clinical examination revealed von Recklinghausen's disease-specific lesions, consisting of soft, round, skin-coloured, pedunculated, fibroids of varying size, located at the facial, abdominal, and posterior thorax level. There have been noted several "café-au-lait" hyperpigmentation spots, round-oval, 2 to 4 cm in size, localized at abdominal and latero-thoracic level, and at axillary level, there were multiple ephelides equivalent to the Crowe sign (figure no. 1). Multiple, well-defined, small-sized, red angiomas, could be seen at abdominal level.

Figure no. 1. Hyper-pigmented, uniform, brownish-coloured, café-au-lait spots, well defined at the level of the axilla (the Crowe sign) and at abdominal level; nodules of soft consistency, skin-coloured at facial level

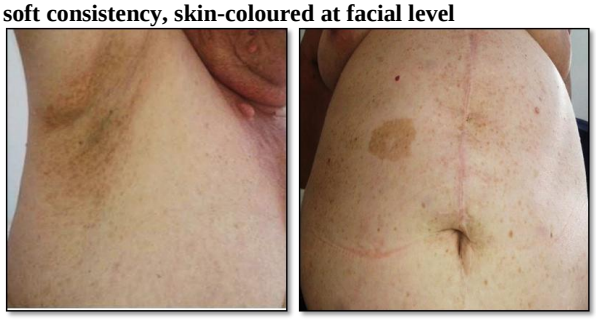

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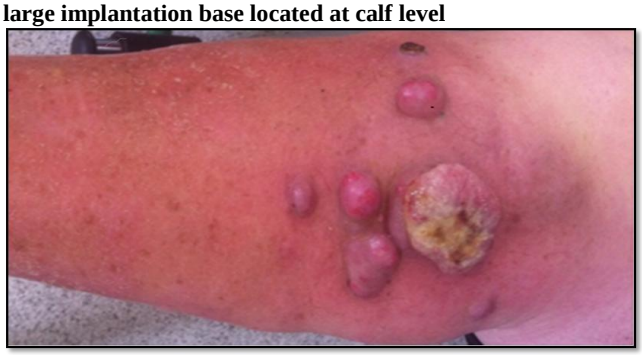
Figure no. 2. Tumour, nodular, achromatic formations, with large implantation base located at calf level



The skin surrounding the tumour masses in the inferior third of the shank showed an erythematous-edematous, infiltrative appearance, with local Celsian signs, with marked pain in the absence of fever and chills (figure no. 2).

Initially, the clinical diagnosis discussed included other skin tumours that could occur in the patients with NF, as follows: neurofibrosarcoma is most commonly considered in a patient with NF1; dermatofibrosarcoma is most commonly located in the trunk, with a slow evolution usually lasting for many years, rarely with metastasis and a characteristic histopathologic appearance of "whirling"; B cell cutaneous lymphoma represents a clonal proliferation of B lymphocytes, which may be limited to the skin or is associated with systemic B cell lymphoma. The immunohistochemical evaluation with B-specific monoclonal antibodies allows the differentiation of pseudolimphoma and other entities; Kaposi's sarcoma in solitary or paucilesional lesions. Of the carcinomas, squamous cell carcinoma, a malignant epithelial tumour developed from the keratinocytes of the epidermis that occurs more frequently in males and develops mainly on pre-existing lesions; basal cell carcinoma may occur in the lower limbs, but the clinical aspects of the multiple, infiltrated tumours, relatively rapid growth ulcers have excluded this diagnosis.

All of these diagnoses were refuted by histopathological examination and special IHC staining.

Achromatic melanoma may be difficult to diagnose by the dermatoscopic examination. There is sometimes a small amount of focal and irregular pigmentation, often at the periphery of the lesion. The atypical vascularization can be a clue, with linear, punctate polymorphs, corkscrew-type. Pink-lactescent areas or globules can be highlighted (95% cases), 43% cases of punctiform vessels, 41% hair-needle, irregular in 49% of cases having a specificity of 84.7% for the achromatic melanoma".(10) Too much pressure through the dermatoscopy tool can hide the vascular model.

The bacteriological examination from the ulcerated nodule has identified the presence of the AchromobacterXylosoxidans bacterium, multi-resistant germ regarding the usual antibiotics. This infection in immunosuppressed patients can cause invasive, severe infections (ulceration, otitis, meningitis, septicemia) with possible progression to sepsis and death. The patient initially underwent antibiotic therapy with first generation cephalosporins until obtaining the result of bacteriological examination after aminoglycoside and carbepenes with favourable evolution of the infection.

Over time, the appearance of the microbial cellulitis of the shank has also expanded at thigh level, requiring antibiotic therapy with long-lasting carbapenems.

The biopsy of a cutaneous form of the shank revealed the presence of nodular proliferation in the dermis, consisting of large-sized cells, predominantly epitheloid and elongate, sometimes arranged in nests (figure no. 3).

The immunohistochemical examination revealed the presence of HMB45-positive in tumour cells and Ki67-30%. These immunomarkers can differentiate between benign and malignant. Benign tumours have less than 6-7% of the marked nuclei. Melanomas that have a proliferation index of> 20% have a reserved prognosis.

These data correlated with the clinical examination with no evidence of the primary skin tumour revealed the diagnosis of skin metastases of malignant melanoma.

Figure no. 3. Histopathological appearance of melanoma metastases

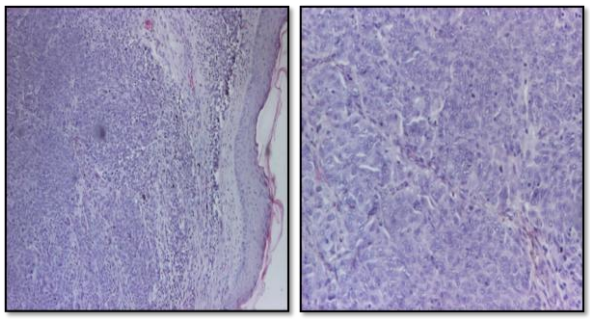
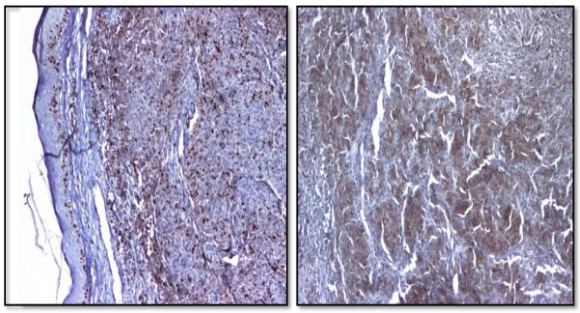


Figure no. 4. Immunohistochemistry of HMB45-positive in tumour cells and Ki 67-30%



The abdominal-pelvic CT performed a short time later revealed a hypodense nodule in the left adrenal gland, a small alveolar area in the right apical segment and right inguinal adenopathies, the largest of which having 3 cm. Cranial CT revealed a parcelar calcification area at the right cerebellum hemisphere and a calcareous conglomerate located in the left cerebellum hemisphere, without indicating signs of cerebral metastases. Pulmonary radiography did not reveal secondary determinations of melanoma. Abdominal ultrasound highlighted fatty liver and enlarged spleen without detectable adenopathies.

The V600E mutation in the BRAF gene provides significant clinical benefits for metastatic MM by the treatment with specific BRAF tyrosine kinase inhibitors. The mutation was present. The BRAF protein plays a key role in regulating the mitogen-activated protein kinase/extracellular signal-regulated kinase MAPK /ERK signalling pathway, one of the most important ways of translating extracellular signals to the nucleus, thus regulating the proliferation, growth and cell survival. BRAF gene mutations occur in 50% of melanomas; 70% -90% are V600E and 10% -30% are V600K.(11)

The patient was taken to the Oncology department where, initially it has been opted for treatment with Dacarbazine 250 mg/mpcu with good digestive tolerance. After performing the BRAF mutation and confirming its positivity, Dacarbazine was replaced with Dabrafenib (BRAF inhibitor) at a dose of 2 x 150mg /day. Dabrafenib treatment is usually administered until the patient no longer presents therapeutic benefits or until major

side effects reactions occur.

The opportunity for surgical treatment was discussed. The presence of local infection with Achromobacter Xyloxidans and the extension of the infection at thigh level associated with septic condition have led to postponing the treatment. Due to the patient's low compliance with treatment, surgery was refused.

Laboratory analyses revealed iron-deficiency anemia, neutropaenia with lymphopenia, increased GGT, elevated erythrocyte sedimentation rate.

DISCUSSIONS

The prognosis for metastatic melanoma with the presence of visceral metastases is reserved. Cutaneous, subcutaneous and extraregional metastases of the lymph nodes (M1a), which were completely resected surgically, have a significantly higher life expectancy than all other localizations, of approximately 23% over 5 years. Visceral metastases (M1c), with the exception of lungs, especially in the brain and liver, develop in most cases to death, with an average survival less than 1 year.(12) The most common cutaneous metastases are the satellites of the primary tumour (up to 2 cm) or in transit, between the tumour and the regional lymph nodes. Occasionally, a metastasis may be heterogeneous, so it is almost impossible to be separated from the primary tumour.

Even though MM represents less than 2% of skin cancers, it is responsible for the majority of the entire skin cancer mortality and incidence has increased rapidly lately. The incidence rate increase differs across continents reaching 3-5% (13) in the European population and 5-7% (14) in the US. Malignant melanoma has a predilection for metastasis in certain organs, so it can disseminate at the skin level between 10-60% cases, lungs 10-40%, 5-45% extra-regional lymph nodes, 2-20% central nervous system, 14- 20%, bone system 4-17%, adrenal glands 1-11%, gastrointestinal tract 1-8%, pleura 5%, pancreas 5%, other organs less than 1%.(1) Diagnosis of melanoma metastasis is set in 10% of cases in the absence of the primary tumour.(15) The results of melanoma metastasis therapy remain unsatisfactory compared to the treatment of other metastatic tumours.

Melanoma is a disease characterized by lesions that activate the extracellular signal-regulated kinase (ERK), which transmits extracellular signals to the nucleus. Approximately 70% of cutaneous melanomas contain mutations that activate the BRAF and NRAS genes, the changes that cause tumour progression are largely undefined. The genomic classification of melanomas according to somatic gene alterations according to Cancer Genome Atlas Network, Cell in 2014 includes 4 subgroups, namely: 47% positive BRAF melanomas, 28% positive RAS, 14% positive NF1, 6% triple wild melanoma.

It is known that NF1 mutations and the loss of NF1 protein expression occur in over 90% of type 1 neurofibromatosis and in over 40% of malignant peripheral nerve sheath tumours (MPNST). Alterations in NF1 protein are common with RAS and BRAF mutations in melanoma. BRAF (V600E) mutation with NF1 protein loss cancels the negative feedback on the RAS gene activation, resulting in high activation of RAS-GTP and RAF resistance sufficient to confer resistance to vemurafenib, but not to MEK inhibitors.(16)

The case differs in its uniqueness as well as in multiple features. In the literature, there are rare reports describing this association. Rubestein et al performed a study of 791 cases of NF, of which 15 cases with giant melanocytic nevi and 4 cases of MM.(17) Brosfield and Das Gyla have published an article on the association between NF1 and MM with a group of 110 patients with NF1 of which 6 associated MM. Both authors have suggested that the concomitant occurrence of these diseases cannot be a coincidence.(18)

The surgical treatment of metastatic melanoma is substituted by the predictive recurrence risk and mortality potential of the surgery. At the local clinical examination, in the case of cutaneous formations on the right leg, the first diagnostic option suggests a neurofibrosarcoma, but the histopathological and immunohistochemical examination revealed malignant melanoma metastases. The patient denied the existence of a suspected lesion that could have indicated a primary tumour. The evolution of the case has been complicated by the association of Achromobacter Xylosoxidans superinfection at the level of the ulcerated tumour lesions and the appearance of thigh cellulitis and sepsis, which has led to postponing the surgical treatment.

Despite the fact that the strategy for the treatment of melanoma has been developed over time, with good results in many clinical trials, patients with MM metastases have survived in very few cases. The drug treatment is used as an adjuvant treatment in unresectable metastatic melanoma and provides only improvements in the survival index. Chemotherapy alone did not demonstrate efficacy in metastatic MM.

Interferon alpha adjuvant immunotherapy has shown that it may increase the disease-free interval, but not the survival, in general. Melanoma metastases do not benefit from radiotherapy. Chemotherapy with Dacarbazine, the most commonly used drug in the last 30 years, has a temporary remission in 5-10% of cases

Dabrafenib is a protein kinase inhibitor indicated in the BRAF V600E mutant melanoma. Trametinib is a MEK inhibitor indicated for melanoma with BRAF V600E or V600K mutations. It is expected that new combinations of specific drugs, such as the combination of Dabrafenib and Trametinib (GSK1120212, a MEK inhibitor), will provide higher response rates and longer-lasting clinical benefits than Dabrafenibmonotherapy. There are no major differences in survival between BRAF /MEK-targeted therapy and PD1 inhibitors immunotherapy, (programmed cell death 1) but both treatments have a higher response rate to chemotherapy.

Vemurafenib in BRAF positive patients and Ipilimumab (ac anti CTDL-4) is the most common strategy for advanced /metastatic melanoma but offers limited clinical benefits. Ipilimumab is preferred in the BRAF-wild type as the first line of treatment.(19)

Nivolumab an Ig4 P-PD1 may result in durable responses in patients who have had favourable progression following treatment with BRAF or Ipilimumab (20)

New treatment prospects are available, the first FDA-approved oncolytic viral therapy, thalimogene laherparepvec (genetically modified herpes virus type 1) is indicated in the local treatment of cutaneous, subcutaneous and nodular lesions in post-surgical recurrence (6) and is designed to replicate in the tumour and to produce granulocyte-macrophage-colony stimulating factor (GM-CSF).

CONCLUSIONS

Early diagnosed malignant melanoma can be excised surgically at minimal costs. Metastatic melanoma generally has an unfavourable prognosis and current medication is very costly.

Special efforts are being made worldwide to improve the prognosis of patients with metastatic melanoma regarding treatment with chemotherapy, biology, or immunotherapy of melanoma. Recent research demonstrates that it is also essential to investigate genotypes in order to choose the best treatment for metastatic melanoma. Long-term prognosis is reserved, with very high mortality and survival under one year, as in the case presented. The diagnosis of achromatic MM was delayed due to

the absence of clinical signs. It is estimated that up to 85% of cases cannot be correctly diagnosed at the time of initial presentation.

The association of metastatic achromatic melanoma with von Recklinghausen's disease is very rare. A multidisciplinary approach is essential in this case, given the difficulty in choosing the treatment for metastatic melanoma.

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