Is histopathological overdiagnosis of melanoma a good insurance for the future?

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'Are we Men or Corporals?' is a 1955 movie in which the Neapolitan actor Totò (Antonio De Curtis; 1898–1967) set Men (those who work very hard and are basically good and simple individuals) against Corporals (those who use their authority and power to make Men's life difficult). Medicolegal concerns are nowadays the Corporals of routine histopathology and dermatopathology. It is well known that the false-negative misdiagnosis of melanoma is the most common reason for claims filed against pathologists [1]. Compared with the disastrous consequences of an unrecognized melanoma, re-excision and sentinel node biopsy, which are the standard procedures for a clinically localized, intermediate thickness melanoma, have negligible consequences because of their very low morbidity; therefore, our Corporals have been increasingly addressing their authority and power toward a more or less conscious approach based on 'defensive overdiagnosis.' The implicit, albeit obvious, assumption is: better living with a diagnosis of melanoma than dying with a diagnosis of nevus. Needless to say, a 'defensive overdiagnosis' automatically translates into a 'defensive overtreatment.'

Figure 1 shows the clinicopathological features of a melanocytic neoplasm removed from the scapular area of a 22-year-old woman. The lesion was histopathologically atypical, and since a single dermal mitosis was detected in one of the tissue sections examined (not shown), the final histopathologic diagnosis was melanoma over nevus, with focal regression, Stage pT1b [2]. The patient underwent re-excision and sentinel node biopsy, the latter showing some MART1 positive cells in the capsule and some HMB45 positive cells within the parenchyma (**Figure 2**). Based on these features, the patient was labeled as having a melanoma micrometastasis (intraparenchymal, tumor burden category <1 mm) [3] of the sentinel node and was therefore candidate to completion dissection of the axillary nodes.

There is no doubt that the whole clinicopathological features of this case are very odd; therefore, and not surprisingly, the Corporals' approach is that offering a young patient a treatment as per melanoma seems to be the surest approach for both the patient and the histopathologist. Nevertheless, we also – if not mainly; or exclusively – have to look at the case

KEYWORDS

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Figure 1. Clinicopathological features of a melanocytic neoplasm removed from the scapular area of a 22-year-old woman. The lesion is larger and more irregular than the other nevi of the patient (A); on dermoscopy, it is asymmetric with a central disruption of the pigment network (B). Histopathologically, the melanocytic proliferation is large, with very irregular silhouette (C); its central area shows a very irregular nested and lentiginous junctional component overlying an area of dermal fibrosis with newly formed vessels and few melanophages (D); a mild pleomorphism is seen in the more superficial dermal melanocytic component, whereas the deep component shows a bland cytomorphology (E). Original diagnosis: melanoma over nevus. Our re-evaluation: the lesion shows the classical ‘trizonal’ pattern ([C–E]: atypical junctional component, dermal fibrosis, bland-appearing deep dermal component) which is described in nevus recurring after incomplete excision (so-called ‘Ackerman’s pseudomelanoma’) [4] or, else, in ‘chronically recurrent nevus’ (so-called ‘sclerosing nevus with pseudomelanomatous features,’ or ‘nevus with regression like fibrosis’ or ‘dysplastic nevus with florid fibroplasia’) [5]. The latter entity typically occurs in the convex area of the back of young patients and is histopathologically identifiable because the fibrosis is:

Figure 1. Clinicopathological features of a melanocytic neoplasm removed from the scapular area of a 22-year-old woman (cont.). different from regression of melanoma (the latter being paler, with untidy collagen bundles, more inflamed and with a greater amount of melanophages); overlying a benign deep dermal, often congenital-like component (regression of melanoma usually being found in *de novo* melanoma and not in nevus-associated melanoma). Revised diagnosis: compound nevus with regression-like fibrosis.

from a different perspective, the one of Men. The proliferation shows the classical ‘trizonal’ pattern (Figure 1C–E: atypical junctional component, dermal fibrosis, bland-appearing deep dermal component) which is described in nevus recurring after incomplete excision (so-called ‘Ackerman’s pseudomelanoma’) [4] or, else, in ‘chronically recurrent nevus’ (so-called ‘sclerosing nevus with pseudomelanomatous features,’ or ‘nevus with regression like fibrosis’ or ‘dysplastic nevus with florid fibroplasia’) [5]. Regarding the sentinel node status (Figure 2), the capsular component is melanocytic (MART1 positive; Figure 2C), but benign because of its location and cytomorphology (Figure 2A). The intraparenchymal pigmented cells are cytomorphologically very bland and different from the dermal component of the primary lesion (Figure 2B vs Figure 1E); moreover, they are MART1 negative (Figure 2D) and therefore are most probably not melanocytes but pigmented macrophages with unspecific absorption of chromogen and or HMB45 antibody (Figure 2F). In summary, according to Men’s approach, the most likely diagnosis is “compound nevus with regression-like features in association with a capsular spindle cell nevus of the sentinel node.”

If it seems that overdiagnosis and overtreatment of melanocytic neoplasms can be our best ‘insurance’ against future medicolegal claims, we all must be also aware that overdiagnosis of melanoma has its own overall cost. In a world in which health care costs are exploiting [6], the damages of an overdiagnosis must be quantified not only and not mainly in financial terms. The nonfinancial damages include: labeling a healthy individual as ‘patient’; discovery of ‘incidentalomas’; and side effects from treatments that have dubious benefit.

The patient’s fear is indeed a higher cost than money expenses themselves. When a healthy

individual becomes a melanoma patient, he/she can receive a significantly negative influence on life decisions such as marriage, pregnancy and investments. A diminished ability to obtain medical insurance and life insurance must be also taken into account [7]. Screening procedures of the patient himself/herself as well as of his/her close relatives can bear further anxiety.

A nodal nevus, like the one shown in **Figure 2**, is a 'pseudomalignant incidentaloma' – which at least complicates the histopathological diagnosis (if it does not lead to further surgery). But 'truly malignant incidentalomas' can also occur: the excision of morphologically malignant but biologically indolent melanocytic neoplasms in the course of screening campaigns for early diagnosis of melanoma has been advocated as one of the major determinants of the so-called 'melanoma epidemics' (an increase in incidence with no increase in mortality for melanoma) [7,8]. And, needless to say, 'truly malignant incidentalomas' have their own additional financial and nonfinancial costs. Further costs are also due to the side effects of (improper) treatments. If it is true that a sentinel node biopsy has very little morbidity, it is also true that its histopathological evaluation may be very difficult [FERRARA G. SENTINEL NODE BIOPSY IN MELANOMA: SOME THEORETICAL ISSUES AND THEIR PRACTICAL IMPLICATIONS (2014), SUBMITTED] and that a histopathological overdiagnosis may be again imposed by our Corporals. Different from the sentinel node biopsy, the completion lymph node dissection may carry significant side effects: for example, the axillary nodal dissection requested for the patient in **Figures 1 & 2**, carries an 'acute' phase (with pain, bruising, infection, seroma, swollen and tight-feeling arm, stiffness, neurosensory changes), followed by possible infectious chronic side effects (erysipela, lymphedema, chronic pain and axillary web syndrome[lymphatic cording]) which can be lifelong and very hard to be effectively treated [9].

Altering our diagnostic definitions and lowering our threshold for a diagnosis of malignancy has led to a greater number of diagnoses and treatments 'for' or 'as per' melanoma; the benefit of the proposed treatments is, however, difficult to demonstrate. Our Corporals maintain that re-excision of melanoma with adequate margins is the mainstay to prevent local recurrence of the disease, whereas sentinel node biopsy is a staging procedure for the detection and the early treatment of occult Stage III melanoma, with the goal of a better/prolonged survival of

Figure 2. Immunomorphological findings in the sentinel node from the melanocytic lesion shown in Figure 1. The nodal capsule discloses a very bland spindle cell population (A), whereas a small collection of pigmented cells is seen within the subcapsular parenchyma (B). The lineage-specific MART1 antibody is positive within the capsular spindle cell component (C), but does not stain the intraparenchymal pigmented cells (D); conversely, the HMB45 antibody does not stain the capsular spindle cells (E), but decorates the intraparenchymal pigmented cells (F). Original diagnosis: melanoma micrometastasis (intraparenchymal, tumor burden category <1 mm) [3] to the sentinel node. Our re-evaluation: there is little doubt that the capsular component is melanocytic (MART1 positive; [C]), but it is benign because of its location and cytomorphology (A) as well as because of its HMB45 negativity (E). The intraparenchymal pigmented cells are cytomorphologically very bland, monomorphic and different from the dermal component of the primary lesion ([B] vs [E]); moreover, they are MART1 negative (D) and therefore are most probably not melanocytes but pigmented melanophages with unspecific absorption of chromogen and/or HMB45 antibody (F). Revised diagnosis: nodal spindle cell nevus with intraparenchymal collection of melanophages.

patients. However, what Men observe in their practice is that most completely excised melanomas recur after many years as multiple foci well beyond the scar edges [10]. Such recurrences have all the features of in transit metastases and, not by chance, often arise synchronously with nodal/distant metastases: intuitively, re-excision of melanoma cannot prevent any metastatic disease. Regarding the therapeutic role of the sentinel node biopsy, a large study on ≥ 1.20 mm-thick melanoma patients randomly assigned to either a sentinel node arm biopsy or an observation arm (Multicenter Selective Lymphadenectomy Trial-1), has shown no significant difference in the 10-year melanoma-specific survival between the two arms [11]. The unique Multicenter Selective Lymphadenectomy Trial-1 finding pointing toward a therapeutic role of the sentinel node is a better 10-year melanoma-specific survival in the subgroup of sentinel-node positive patients compared with the relapsing patients of the observation group ($62.1 \pm 4.8\%$ vs $41.5 \pm 5.60\%$) [11]; such a subgroup analysis, however, was not generated on randomized patients and is therefore of doubtful statistical value [FERRARA G. SENTINEL NODE BIOPSY IN MELANOMA: SOME THEORETICAL ISSUES AND THEIR PRACTICAL IMPLICATIONS (2014), SUBMITTED]. Thus, to date, sentinel node biopsy is a merely staging procedure with a negligible impact on the overall survival of melanoma patients.

For all the above, we can conclude that in the field of morphologically controversial melanocytic proliferations, our Corporals support the use of surgical procedures which Men readily recognize as having little usefulness even for patients with a clear-cut melanoma. Moreover, the Corporals' logic is indeed an ominous 'insurance for our FUTURE': when dealing with difficult-to-diagnose lesions, the more we encourage an aggressive management in the PRESENT, the more we are prone to medicolegal concerns for our mistakes of the PAST.

The strategy to face with Corporals' rules is not to be ready to overdiagnose melanoma in case of doubt, but to keep being Men: human beings cannot be inerrable, but they must spend any effort to avoid erring. The simple rules are:

- Never finalize any report under a H.A.L.T. (hungry, angry, late, tired) condition;
- Make sure that all the pertinent clinical information, comprising the clinical diagnosis, will be provided in the final histopathological report;
- Always achieve step sections for controversial cases;
- Thoroughly report the microscopic features of a controversial case along with the differential diagnoses raised; always discuss the original diagnosis in a 'second opinion' setting;
- Submit any controversial case for intradepartmental and interdepartmental consultation;
- Explicitly refer to a multidisciplinary meeting for further clinicopathologic evaluations and for any decision about the management;
- Deliver a supplementary report for any diagnostic opinion achieved both in a consultation and in a clinicopathological setting.

Our 'insurance for the future' is not to undergo authoritarian Corporals, but to behave as authoritative Men.

Future perspective

Defensive overdiagnosis and overtreatment of melanocytic skin neoplasms is expected to increase in the next future. The adoption of honest and thoughtful guidelines for morphologically equivocal melanocytic neoplasms will eventually defeat the more or less conscious decision to manage all these lesions as per melanoma of the same thickness.

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