Clinicopathologic Dissociation in Dermat[onc]ology – and Beyond

Giovanni Luigi Capella*

Dermatology & STD, Milan, Italy

Abstract: The concept of clinicopathologic dissociation is a neglected one in medicine. It refers to the unexpected, complete absence of concordance between the clinical picture and the underlying histopathologic finding. The recognition of such a phenomenon generally implies radically different treatment and follow-up choices. A rare phenomenon, it can however be encountered, especially in the field of dermatoncology and dermatology at large. It should be kept separate from clinicopathologic discordance or discrepancy, the term used by surgical pathologists to indicate the lack of expected molecular markers or to the presence of unexpected ones in the face of a given morphological diagnosis, albeit overlaps occur. More generally, the concept of clinicopathologic dissociation can be applied when a given clinical manifestation appears completely unrelated to the underlying objectively tracked primary disease. Examples are provided, and educational, ethical and medicolegal implications are briefly discussed.

Keywords: Clinicopathologic dissociation, Clinicopathologic discordance, Clinicopathologic discrepancy, Clinicopathologic correlation, Mimicker, Misdiagnosis, Diagnostic errors.

INTRODUCTION

A quarter century ago, the author visited a patient complaining of a plaque lesion of the forehead – an unusual site, but the clinical aspect was that of *dyskératose lenticulaire en disque* [1], quite typical for Bowen's disease. A biopsy was performed. The physician was quite confident of his clinical diagnosis, but was astonished by the pathologist's report, that spoke of granulomatous rosacea. The patient was happy (his "tumour" cleared after a 3-month course of oral tetracycline and topical metronidazole), your author, too – on a human level, of course: less on the intellectual one! The pathologist was qualified and reliable, slides were reviewed, identification errors [2] were excluded, the case was collegially discussed… No way: the clinical aspect and the histological picture did not match. How could it happen that an inflammatory condition mimicked a typical carcinoma in situ so strictly, so defiantly? Thus started the author's interest in this puzzling, yet neglected, or even plainly unrecognised phenomenon.

THE PROBLEM: "DISCREPANCIES", "INCONSISTENCIES", "MIMICKERS", & CO.

The terms "clinicopathologic discordance/ discrepancy/ inconsistency" are widely and rather loosely used, especially by surgical pathologists. Mostly, they refer to the lack of expected molecular markers or to the presence of unexpected ones in the face of a given morphological diagnosis, with special reference to differentiative and histogenetic processes. This can be the case, for example, of the divergent expression of MUC glycoproteins and the putative CDX-2 tumour suppressor in Barrett oesophagus samples featuring microscopical aspects of dysplasia and intramucosal carcinoma [3]. Instead, to the best of author's knowledge, the term "clinicopathological dissociation" (an alternative could be "clinicopathologic decoupling") is underrepresented in medical literature. Accordingly and provocatively, the author decided to include the term in the list of the key words of this paper. It could be defined as *the unexpected, complete absence of concordance between the clinical picture and the underlying histopathologic finding. The recognition of such a phenomenon generally implies radically different treatment and follow-up choices.* By "unexpected" it is meant that the definite diagnosis generally belongs to a quite unrelated differential-diagnostic cluster (exceptions admitted, of course! See below). An element of absolute surprise is inherent in the definition: an example could be a congenital smooth muscle hamartoma clinically presenting as a vascular lesion, a finding labelled with the usual, yet vague (see above) term of "clinicopathologic discordance" by the scholars who have described it [4]. These authors use the term only in the title, and it turns out as implicitly amenable to attributes such as "clinically mimicking" or "masquerading" elsewhere in the title and in the body of the paper. An explicit definition lacks.

As to the quoted, obliged "surprise effect", the shift to an unrelated differential-diagnostic cluster should be virtually mandatory, but we are in the realm of exceptionality, and exceptions rule. For instance, apart from most atypical cases (which exist!), the concept of clinicopathologic dissociation does not generally apply

*Address correspondence to this author at the Dermatology & STD, 7 Via Sant'Alessandro Sauli, 20127 Milan, Italy; Tel: +39-(0)2-2822542;
E-mail: progderm@katamail.com

ISSN: 1929-2260 / E-ISSN: 1929-2279/22 © 2022 Neoplasia Research

to seborrheic keratosis-like melanoma, which, albeit rare, is recognized and sufficiently codified in the current nosography [5]. Both entities belong to the same differential-diagnostic cluster, namely, focal pigmented lesions (a cluster which includes also pigmented pagetoid basal cell carcinoma versus pigmented Bowen's disease; or extended solar lentigo versus lentigo maligna), and the very fact a lesion underwent reflectance confocal microscopy and/or excision implies that there was something wrong in that "seborrheic keratosis" at a clinical-dermoscopic level. However, beyond these unclear lesions, sporadic residual ones exist, which display genuine clinicopathologic dissociation in this setting. In the author's experience, this is especially true of traumatized lesions, which can resemble trivial seborrheic keratosis (focal residual islands) to an extent precluding the appreciation of clinical and dermoscopic clues of melanoma. The case for melanoma mimicking plantar wart is akin [6].

Other examples of clinicopathologic dissociation in dermatoncology are the prodromic, treacherous ecchymotic phase of angiosarcoma (which, when full-blown, is nodular-ulcerative); synovial mycosis fungoides presenting as rheumatoid arthritis [7]; and the so called "invisible dermatoses". This term is unfortunately ambiguous, being used in two different senses: clinically relevant skin lesions that lack evident, unless painstakingly searched, histologic correlates [8]; and skin diseases without clinically evident lesions but showing histologic changes of specific nature: this is especially the case of occult mycosis fungoides [9] and mastocytosis [10]. The second connotation of the term is of interest for us. However, we have to admit that this clinicopathologic dissociation is not absolute, in that these patients complain of itch, which focuses the attention of the diagnostician. The criteria of chronicity, evolutivity, and resistance to symptomatic treatments are the best indices of suspicion.

The field of skin lymphoproliferative and histiocytic lesions allows less and less room to the concept of clinicopathological dissociation. Experts are accustomed to the "surprise effect" (T-cell reactive infiltrate accompanying B-cell leukemia cutis clinically mimicking mycosis fungoides [11]; polyclonal S100 positivity with CD1a negativity in progressive nodular histiocytosis [12], aberrant phenotype transition, etc.). At the end of the day, they operate in the sphere of a fixed, highly characterized, however variegated differential-diagnostic cluster. To tell the truth, the vast majority of the discrepancies they encounter is amenable to the concept of clinicopathologic discordance in the sense of surgical pathologists (see above)

In general, it would be the microscopic diagnosis (the surprise!) to prevail and indicate the correct prognostic and therapeutic path, but the reverse can be true. A report about gastrointestinal reflux disease disguising as eosinophilic esophagitis [13] is interesting, not only because it is the only example of the use of the term "clinicopathologic dissociation" in the literature. Rather, it is a proof of concept that *in clinicopathologic dissociation not necessarily the histopathologic finding dictates the definitive diagnosis.* Indeed, in the described cases the response to proton-pump inhibitors evidenced that the clinical diagnosis was the right one, and prevailed over the microscopic correlate. However, this statement is better suitable to the domain of inflammatory and dysfunctional conditions, rather than of oncologic ones, where histopathology has generally the final say.

In the absence of appreciable, definite lesions, the problem is different when the inconsistency does not depend on imitation, rather on an apparently complete lack of correlation: a typical case is pancreatic cancer presenting as acute depression [14], a time-honoured [15], yet often unrecognised association. Here the clinicopathologic incoherence seems absolute, and the link between the two conditions is putatively biochemical (depressing effect of cancer-derived kynurenine? [16]). Biochemical processes always precede morphologic manifestations, and represent the invisible bridge connecting apparently unrelated clinical and histological findings. From this viewpoint, most paraneoplastic syndromes should be regarded as examples of clinicopathologic dissociation – until they are recognised and nosographically codified, at least, because many of them *do display* a specific intrinsic histopathologic correlate, which reveals the link to the underlying neoplasia. Note that this concept implies the recognition of a *specific* clinical picture which cannot be related to the anatomopathological structure of the underlying primary noxa (otherwise, we could label as cases of clinicopathologic dissociation all cases – say – of fever of unknown origin: *en voulant embrasser tout, on embrasse trop*). A similar case is that of swan-neck joint deformity of the hands consequent to Parkinson's disease and imitating rheumatoid arthritis [17]. It was described in 1864, but its pathogenesis remains unknown.

Obviously, the clinicopathologic dissociation concept does not apply to misdiagnosis and diagnostic

traps, such as leprosy for dermatologists practising outside endemic areas [18]; ichthyosform sarcoidosis; psoriasiform or lichenoid secondary syphilis... Terms such as “mimickers”, “masquerading” or “disguising as” should be probably reserved to these contexts. Notwithstanding, one could glimpse a continuous spectrum between the two extremes represented by plain misdiagnosis and genuine clinicopathologic dissociation. An alternative key to understanding this spectrum is as follows: when a mimicker is perceived as such because of plainly subjective reasons (premature closure bias, inexperience, or lack of knowledge) we are on the far end of the spectrum corresponding to misdiagnosis (e.g., pagetoid basal cell carcinoma mistaken for nummular eczema or herald patch of pityriasis rosea); when the intrinsic structure of the mimicker is objectively misleading, we are on the opposite side of the spectrum, that corresponds to clinicopathologic dissociation. A thorny item in this sense is represented by melanoma incognito, to wit, a lesion which displays the histological pattern of melanoma, but appears quite unspecific clinically, resembling a pimple or an insect bite [19]. This topic has already been tackled by the author. Elsewhere [20] he has implicitly highlighted the risk inherent in the wild application of the concept of clinicopathologic dissociation in the setting of extensive mass surveillance aimed at the early diagnosis of a specific kind of neoplasia. It must be underscored that clinicopathologic dissociation is an exceptional phenomenon, and that the unfounded assumption it could frequently underlie any trivial lesion could lead to the explosion of oversized invasive medical checks in the frame of defensive medicine (clinicopathologic dissociation becoming a synonym for “widespread malpractice related to a peculiar variant of misdiagnosis”), or even of deliberate purpose of inappropriate extension of not validated screening or surgical procedures for commercial reasons. The same applies to unspecific macular and papular lesions of the face. It is true that retrospective analysis based on reflectance confocal microscopy demonstrated that some of these lesions were “invisible basal cell carcinomas” [21], but it is also true that clinicopathological dissociation cannot be precautionally invoked or suspected in *all* of these cases. The criterion of evolution must be considered (see above, about the invisible dermatoses; and below, “rule of thumb”), unless we are keen on founding a highly questionable industry base on mass confocal microscopy screenings of pinpoint Miescher’s naevi and closed comedones!

BACK TO INTRODUCTION - REVISITED

In the current dermatologic environment, a typical trick of the trade of congress or CME course keynote speakers is to produce a banal-looking lesion and, after an excruciating dermoscopic tour-de-force, to terrify the audience with a surprising histologic diagnosis of a "what-a-good-chap-I-am: it was melanoma": a well concocted example of “dermoscopy-patologic dissociation”! The correct approach would be to produce concurrently several pictures of banal-looking lesions occurring in the same kind of "high risk patients with multiple naevi", to explain why attention was focused on the excised lesion, and why the others were not cut away - or frankly tell how many others were or had been! Instead, the “experts” retrospectively choose the frightening banal-looking case among the results of several biopsied benign lesions. These exercises are tricky: it turns out easy to impute the "correct" diagnosis ex post to nearly invisible dermoscopic features. The author does not want to follow such examples of malice, but, in retrospect, would like to try an explanation of his historical case. Is it truly paradoxical that granulomatous rosacea can display a clinical pattern of apparent Bowen’s disease? Paul Gerson Unna, the founder of modern dermatopathology, warned: evaluate the histological picture with a clinically trained eye – and evaluate the clinical picture with a microscopically trained eye [22]. Could the author have applied this recommendation to reach the correct diagnosis? The clinical diagnosis of Bowen’s disease is not always straightforward. The differential includes – among others – verrucous tuberculosis and tertiary syphilis [1]: coincidentally, two granulomatous diseases! It must be recalled that, in the age of flourishing tuberculosis, several disease patterns now considered as variants of rosacea were considered as expressions of underlying TB: this is the case of lupus miliaris disseminatus faciei and of rosaceiform tuberculides of Lewandowsky. As a matter of principle, it is conceivable that confluent lesions of granulomatous rosacea confined in a possibly traumatized seborrheic area (forehead) could produce a polycyclic pattern covered by a fleeting irregular layer of unspecific desquamation, thus deceiving the diagnostician’s eye. In contrast to the claims of vain dermoscopists and other false diagnosticians who affirm they had clinically recognised that lesion whereas they were already aware of the pathologist’s report, the author dares to absolve himself. It would have been unfair to demand a resolutive *a priori* application of Unna’s rule. Notwithstanding, a retrospective reconsideration of the case tells us that

"clinicopathologic dissociation" could be an apparent phenomenon, only related to the limitations of the codified nosographic and morphologic models we apply in our daily practice. Nevertheless, real-world diseases don't read medical textbooks, which often simply repeat the information printed in previously published ones, [23], and can baffle the updated knowledge we boast about. From this viewpoint, the concept of "clinicopathologic dissociation" could go hand in hand with that of pathomorphosis, the progressive variation in the clinical and anatomical expression of a disease, as well as of its morbidity and mortality, induced by local, therapeutic, social and historical factors – but we'll reserve this topic for another essay!

A CAVEAT TO CONCLUDE

Most cases of "mimickers" with absolute clinicopathologic inconsistency remain isolated curiosities. Apart from few recurrent, codified cases, duplicates of such odd observations are exceptional. Thus, the significance of such reports remains limited as to their practical importance, yet the study of these cases acts as an unvaluable educational warning. Overconfident clinicians are often blamed for acting hastily. "Next time, it could be the morgue" turns out as a logical consequence of such an attitude that easily misses the diagnosis of dangerous diseases presenting in atypical forms. This does not mean that physicians, especially young ones, are to be pushed to become hesitant to give their diagnostic judgement – far from it! A useful rule of thumb follows: most atypical cases of progressive diseases are doomed to qualify if accurately and timely followed-up; monitor conservatively, but, in case of doubt, don't hesitate to recur to aggressive work-up.

The expectation from the society of "zero diagnostic error" and the "zero error standard" supported by the US and other judicial systems is unattainable for several obvious reasons [2]. Apart from procedural errors or even egregious diagnostic blunders, it is intrinsic to medicine the fact we try to reduce uncertainty, but that we cannot get it to zero. [24] The concept of clinicopathologic dissociation is an awkward one, and surely sounds incomprehensible to the public and suspect to jurists and medicolegal experts. What would have happened if the anecdotal case of the author had presented in reversed terms (genuine Bowen's disease disguising as rosacea granulomatosa)? That's why the author expresses his hope the recognition of such a concept will be taken in due account as an exceptional, yet inescapable contribution to this state of things, which stems from a simple fact: our knowledge of medicine, no matter how advanced, will remain always limited, as our human nature is. It is reiterated: "exceptional", according to our daily experience as practising physicians and to common sense. In an age of overeager patients, browsing the Internet in order to find implausible "causes" of their discomfort, the fear that clinicopathologic dissociation could underlie every trivial dermatologic (but not only) complaint, could overburden medical care systems, encourage unethical practices, and ultimately do harm to the patients themselves.

REFERENCES

[1] Degos R. Dermatologie. Paris, Flammarion, 1983; pp. 834-8.

[2] Freire Santana M, de Lima Ferreira LC. Errors in surgical pathology. In: Zaman G, ed. Quality Control in Laboratory. London, IntechOpen, 2018; pp. 89-107. https://doi.org/10.5772/intechopen.72919

[3] Khor TS, Alfaro EE, Ooi EMM, Li Y, Srivastava A, Fujita H, Park Y, Priyanthi Kumarasinge M, Lauwers GY. Divergent expression of MUC5AC, MUC6, MUC2, CD10, and CDX-2 in dysplasia and intramucosal adenocarcinomas with intestinal and foveolar morphology: is this evidence of distinct gastric and intestinal pathways to carcinogenesis in Barrett esophagus? Am J Surg Pathol 2012; 36: 331-42. https://doi.org/10.1097/PAS.0b013e31823d08d6

[4] Schrom KP, Shah SD, Rohr B. Clinicopathologic discordance: Congenital smooth muscle hamartoma clinically mimics reticulated vascular lesion. JAAD Case Reports 2022; 26: 9-12. https://doi.org/10.1016/j.jdcr.2022.05.036

[5] Janowska A, Oranges T, Iannone M, Romanelli M, Dini V. Seborrheic keratosis-like melanoma: a diagnostic challenge. Melanoma Res 2021; 31: 407-12. https://doi.org/10.1097/CMR.0000000000000756

[6] Mc Burney EI, Herron CB. Melanoma mimicking plantar wart. J Am Acad Dermatol 1979; 1: 144-6. https://doi.org/10.1016/S0190-9622(79)70012-0

[7] Sandberg Y, El Abdouni M, Lam KH, Langerak AW, Lugtenburg PL, Dolhain RJEM, Heule F. Clonal identity between skin and synovial tissue in a case of mycosis fungoides with polyarthritis. J Am Acad Dermatol 2004; 51: 111-7. https://doi.org/10.1016/j.jaad.2004.01.043

[8] Brownstein MH, Rabinowitz AD. The invisible dermatoses. J Am Acad Dermatol 1983; 8: 579-88. https://doi.org/10.1016/S0190-9622(83)80078-4

[9] Pujol RM, Gallardo F, Llistosella E, Blanco A, Bernadò L *et al*. Invisible mycosis fungoides: a diagnostic challenge. J Am Acad Dermatol 2000; 42: 324-8. https://doi.org/10.1016/S0190-9622(00)90103-8

[10] Ludolph-Hauser D, Schöpf P, Rueff F, Przybilla B. Okkulte kutane Mastozytose. Hautarzt 2001; 52: 390-3. https://doi.org/10.1007/s001050051330

[11] Metzman MS, Stevens SR, Griffiths CEM, Ross CW, Barnett JM, Cooper KD. A clinical and histologic mycosis fungoides simulant occurring as a T-cell infiltrate coexisting with B-cell leukemia cutis. J Am Acad Dermatol 1995; 33: 341-5. https://doi.org/10.1016/0190-9622(95)91430-7

[12] Glavin FL, Chhatwall H, Karimi K. Progressive nodular histiocytosis: a case report with literature review, and

discussion of differential diagnosis ad classification. J Cut Pathol 2009; 36: 1286-92. https://doi.org/10.1111/j.1600-0560.2009.01454.x

[13] Yılmaz Ö, Ertoy Karagöl Hİ, Topal E, Ünlüsoy Aksu A, Eğritaş Ö, Işık Gönül İ, Bakırtaş A. Clinicopathologiical dissociation in isolated esophageal eosinophilia. Turk J Gastroenterol 2014; 25 (suppl. 1): 276-7. https://doi.org/10.5152/tjg.2014.6326

[14] Boyd AD, Ra M. Depression and pancreatic cancer. J Natl Compr Canc Netw 2007; 5: 113-6. https://doi.org/10.6004/jnccn.2007.0012

[15] Yaskin J. Nervous symptoms as earliest manifestations of cancer of the pancreas. JAMA 1931; 96: 1664-8. https://doi.org/10.1001/jama.1931.02720460010003

[16] Botwinick IC, Pursell L, Yu G, Cooper T, Mann J, Chabot JA. A biological basis for depression in pancreatic cancer. HPB (Oxford) 2014; 16: 740-3. https://doi.org/10.1111/hpb.12201

[17] Harris ED Jr. The clinical features of rheumatoid arthritis. In: Kelley WN, Harris ED Jr., Ruddy S, Sledge CB. Textbook of Rheumatology, 3rd ed. Philadelphia-London, Saunders, 1989; pp. 943-81.

[18] Rongioletti F, Gallo R, Cozzani E, Parodi A. Leprosy: a diagnostic trap for dermatopathologists in non endemic area. Am J Dermatopath 2009; 31: 607-10. https://doi.org/10.1097/DAD.0b013e3181a105a1

[19] Argenziano G, Zalaudek I, Ferrara G, Johr R, Langford D, *et al.* Dermoscopy features of melanoma incognito: indications for biopsy. J Am Acad Derrmatol 2007; 56: 508-13. https://doi.org/10.1016/j.jaad.2006.10.029

[20] Capella GL. Do "incidental melanomas" exist? If so, how many are they? High time to decide. J Cancer Res Updates 2019; 8: 56-9. https://doi.org/10.30683/1929-2279.2019.08.08

[21] Ruini C, Hartmann D, Saral S, Krammer S, Ruzicka T, von Braunmühl T. The invisible basal cell carcinoma: how reflectance confocal microscopy improves the diagnostic accuracy of clinically unclear facial macules and papules. Lasers Med Sci 2016; 31: 1727-32. https://doi.org/10.1007/s10103-016-2043-3

[22] Herrmann F. Oscar Gans zum 65. Geburtstag! Hautarzt 1953; 4: 95-6.

[23] Jacoby RA, Kucer K. Diseases don't always read the textbooks! Dermatopathol Pract Concept 1996; 2: 110-1.

[24] Barondess JA. The impossible in medicine. Perspect Biol Med 1986; 29: 521-9. https://doi.org/10.1353/pbm.1986.0046

Received on 24-07-2022 Accepted on 17-09-2022 Published on 22-09-2022

https://doi.org/10.30683/1929-2279.2022.11.01

© 2022 Giovanni Luigi Capella; Licensee Neoplasia Research.
This is an open access article licensed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/) which permits unrestricted use, distribution and reproduction in any medium, provided the work is properly cited.