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CONTROVERSIES IN DERMATOLOGY

Recent Data on the Risk of Malignancy in Congenital Melanocytic Nevi: The Continuing Debate on Treatment

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Abstract. Congenital melanocytic nevi (CMN) have traditionally been considered a risk factor for the appearance of melanoma, but the true incidence of malignancy is unknown. Although various studies have attempted to quantify it, the results are highly variable and it is difficult to decide on the best therapeutic approach to take. Consequently, for some time the management of CMN has depended more on personal experience than on clear scientific evidence. The most recent studies performed in large patient series indicate that the risk of malignancy in CMN is much lower than expected and mainly affects large lesions involving the axial midline. In addition, it appears that a number of melanomas develop on the site of partially or completely excised lesions, or even away from the CMN itself, making the appropriateness of prophylactic surgery increasingly doubtful.

Key words: congenital melanocytic nevus, melanoma, risk.

ÚLTIMOS DATOS SOBRE EL RIESGO DE MALIGNIZACIÓN DE LOS NEVUS MELANOCÍTICOS CONGÉNITOS: EL DEBATE SOBRE EL TRATAMIENTO CONTINÚA

Resumen. Los nevus melanocíticos congénitos (NMC) se han considerado tradicionalmente un factor de riesgo para la aparición de melanoma, pero se desconoce la verdadera incidencia de la malignización. Aunque numerosos trabajos han tratado de cuantificarla, los resultados son muy dispares y resulta difícil decidir qué actitud terapéutica es la más adecuada. Por este motivo, durante mucho tiempo el manejo de los NMC ha dependido más de la experiencia personal que de una auténtica evidencia científica. Los últimos estudios realizados en series amplias de pacientes reflejan que el riesgo de malignización de los NMC es mucho más bajo de lo que se creía, y afecta principalmente a lesiones de gran tamaño localizadas sobre el axis. Además, parece que un considerable número de melanomas se desarrolla sobre lesiones parcial o totalmente extirpadas, e incluso fuera del propio NMC, por lo que la necesidad de la cirugía profiláctica es cada vez más controvertida.

Palabras clave: nevus melanocítico congénito, melanoma, riesgo.

Congenital melanocytic nevi (CMN) are benign melanocytic proliferations that are present from birth. Traditionally, these lesions have been classed as small (<1.5 cm), medium (1.5-20 cm), or large (>20 cm),[1] although the category of giant CMN has been proposed recently for lesions that measure more than 40 cm in diameter.[2] Morphologically, giant CMN are often described as "garment nevi," displaying a "garment-like" pattern, where the specific description (shirt, pants, bathing trunks, cuffs, etc) refers to the site. CMN can appear as individual or multiple lesions. A larger nevus may be surrounded by smaller ones (satellite nevi) whereas in other cases, no single CMN is markedly larger than the others (multiple CMN). Patients with CMN have more melanocytes than normal, and so there is a greater risk that some of these will undergo malignant transformation. A number of studies have attempted to quantify this risk, but in view of the very variable results, it is difficult to decide on the most suitable therapeutic approach. Whereas some authors propose prophylactic excision of the lesions to minimize as far as possible the potential risk, others favor a wait-and-see approach because surgery is associated with a high level of morbidity, it is often impossible to eliminate all nevus cells, and the melanoma may develop at a site other than the CMN itself.

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The differences in opinion have led to passionate debates with the result that the treatment the patient receives is determined by the opinion of the specialists involved.

It is calculated that between 0.2% and 2.1% of newborn infants have CMN.[3,4] As in other uncommon processes, it is difficult to obtain homogeneous data from a large number of affected patients, analyze these data prospectively over a long period, and draw statistically significant conclusions on the biological behavior of the lesions. Fortunately, in recent years, studies of CMN of increasing scientific validity have been published, in some cases through the use of online registries.[5-11] Some of these studies were included in an extensive systematic review published in 2006.[12] That review analyzed the clinical characteristics and risk of developing melanoma from CMN in a very broad population group with a relatively long follow-up and, in some respects, reached novel conclusions that we thought worthy of comment in this article.

For the systematic review, the authors searched for all studies indexed in MEDLINE between 1966 and 2005 with the terms "nevus" and "congenital" and "melanoma" or "malignant" or "malignancy" or "risk." The authors only included systematic series of more than 20 patients with a follow-up of more than 3 years (the mean duration was between 3.4 and 23.7 years); the 14 series that met these criteria included a total of 6571 patients, in whom 46 cases of melanoma were detected (0.7% of the cases). The sample size—ranging from 39 to 3922 cases—had a strong influence on the risk observed, which ranged from 0.05% in the largest series[3] to 10.7% in the smallest[13]; of note was the fact that the incidence of melanoma did not increase with longer follow-up and that the series with the longest follow-up periods did not report higher rates of malignancy. The mean and median ages of these patients at the time of diagnosis were 15.5 years and 7 years, respectively. The estimated relative risk of appearance of melanoma during childhood and adolescence was 465 times greater in patients with CMN than in the rest of the population.

With regard to size, only 9 of the 14 series specified the number of large CMN; of the 1539 patients included in those 9 series, 39 had a melanoma in a large CMN, corresponding to a specific frequency of 2.5% for this subgroup. The only 3 series that specified the number of giant (or garment) CMN reported malignancy in 3.1% of such lesions, that is, the incidence of melanoma is greater in larger CMN than in the overall group, in which it was 0.7%. The authors of the review also analyzed the size of CMN in which the melanoma occurred and found that in 30 of the 41 cases (73%) in which this information was available, the lesion that had undergone malignant transformation was a giant or garment CMN, whereas in the other 5 cases (12%), the CMN were classed as large. In 67% of the cases, the melanomas appeared in the CMN themselves (33 cases), whereas in the remaining third they developed at an extracutaneous site (8%) or originated from an unknown site (14%). There were cases in which the melanoma appeared in the region where the CMN had been completely or partially excised.[6] As for prognosis, the overall mortality was 50%. Of the 33 cases in which the melanoma developed in the CMN itself, 11 (33%) had a fatal outcome. Life expectancy was markedly worse in individuals with giant CMN (mortality of 63%) than in patients with large CMN (mortality of 20%). Other findings of interest were that some of the published series only reported malignancy in those nevi at sites on the axial midline,[5,6] and there was only 1 case of malignant transformation in a satellite lesion.[6] The authors of the review concluded that clinical data on patients must be collected consistently to enable the findings to be validated in view of the notable variation in the clinical characterization, histologic data, age at inclusion in the studies, follow-up duration, and definition of complications such as neurocutaneous melanosis.

The results obtained in that review are particularly pertinent in certain aspects such as the incidence of malignancy, the age at presentation and the origin of the melanoma, and the clinical characteristics of the CMN that had undergone malignant transformation. The risk of malignancy was 0.7%, confirming the suggestion of a number of authors in recent years that the probability of the appearance of melanoma in a CMN is lower than initially thought.[3,6,10,11,14] The fact that the smallest series reported a much higher risk is probably due to a selection bias in large referral centers and in retrospective studies where only the most difficult cases are seen or referred. In any case, the authors found that these patients have a relative risk of malignancy approximately 465 times greater than the normal population, an observation which seems reasonable if we remember that the risk of malignant transformation increases with increasing numbers of nevus cells. On the other hand, while it is true that the follow-up period was not particularly long in any of the series and that perhaps some of these patients might have developed melanoma after follow-up had finished, there were no significant differences in incidence between the shorter and longer periods of follow-up. According to the authors of the review, this shows that the development of malignancy does not depend solely on the passage of time but that it is also contingent on additional factors such as CMN size and the age of the patient, for example. In this respect, they also provided further novel data in that, unlike a previous review which suggested that the risk of malignancy peaked in the first 3 years of life and that early childhood was the ideal time for prophylactic treatment,[15] the recent systematic review found that the critical periods for developing malignancy were when the children were of school age and adolescents. The authors highlighted that most of the studies provided information on pediatric patients and so there could be an age-selection

bias favoring this theoretical tendency for malignant transformation early in life.

The clinical characteristics that were reported to be relevant included size of CMN that had undergone malignant transformation, their location, and the behavior of satellite nevi. The risk of melanoma in the series that specifically analyzed large and giant CMN was substantially greater than that observed in series that included lesions of all sizes, and when the specific characteristics of the CMN that had undergone malignant transformation were analyzed, most of them (85%) were large or giant CMN. Not enough information was available on nevus size in all cases of malignant transformation, but it is of note that the largest study, which included 3922 patients, did not detect malignancy associated with any small CMN.[3] As a result, according to the findings of that study, patients with large CMN are the ones most at risk of developing melanoma. The authors recognized, however, that small CMN may have received less attention in epidemiologic studies than those of larger size, and so the true risk associated with small CMN may have been underestimated. In daily clinical practice, melanomas are diagnosed relatively often in a nevus that a patient claims to have had ever since birth. Similarly, melanocytic nevi often show a congential histologic pattern in the pathology report. These observations seem to provide evidence that malignancy might be associated with small CMN, but the patient may be mistaken about when the nevus appeared (children and even adolescents do not pay much attention to pigmented lesions and they may interpret an acquired nevus that appears in the first years of life as a congenital lesion) and the difficulty of establishing the time of appearance of melanocytic nevi according to exclusively histologic criteria is well documented.[16] The size of CMN that underwent malignant transformation was also an important prognostic factor as mortality was much higher for giant CMN than for other CMN, thereby confirming the importance of nevus size both for risk of malignant transformation and for survival when melanoma develops. Almost all malignant CMN were located on the axial midline region of the trunk, particularly in the case of nevi displaying a garment-like pattern. This site is also of particular interest for the detection of neurocutaneous melanosis,[7,17] something which has prompted some authors to suggest a certain pathophysiologic link between the 2 processes.[18] Finally, although the presence of satellite nevi is also a known risk factor for neurocutaneous melanosis,[9] and even for melanoma,[11] only 1 case of malignancy of a peripheral lesion has been reported,[6] and so in practice, such malignancy seems to be an exception.

Another important observation is related to the origin of the malignant cells, which do not necessarily arise in the region of greatest melanocyte concentration. It is therefore noteworthy that 22% of patients developed melanoma outside the CMN, and that there were several cases in which the melanoma appeared in the same region where the CNM had been completely or partially excised. That is, patients who are born with CMN may not only develop melanoma in this lesion but also at other sites, and radical excision of the pigmented lesion, if possible, does not eliminate the risk of malignancy, even on a local level. Furthermore, regular visual examination of the pigmented lesion may not be sufficient for early detection of malignant transformation in these patients, as malignancy can develop in muscle, the peritoneal cavity, fasciae, or the central nervous system, and may even start as a metastasis of unknown origin.[12]

Some authors do however advocate prophylactic excision of CMN.[19] Their rationale is that the substantial relative risk of developing melanoma justifies eliminating as many nevus cells as possible even though most patients with CMN never develop melanoma. In fact, although cases have been reported of melanoma developing in a partially excised CMN, many more patients who did not undergo such as operation have developed melanoma,[15,19] and so a certain protective effect of surgery cannot be ruled out. Likewise, the CMN site would not influence these authors when deciding whether to proceed with surgery, as nevus cells are the same and have the same malignant potential wherever they are located (head, limbs, or trunk). Intuitively, it might be thought that the risk of malignancy is lower when fewer nevus cells are present in a given individual, and so surgery may provide protection for patients. According to this argument, the effect should be greater the earlier that surgery is performed, but we should remember that radical excision of large CMN is associated with substantial surgical morbidity and usually gives poor aesthetic results.[20] In any case, the final conclusion of the authors most strongly in favor of this approach does not differ that much from the conclusions of studies in which a conservative approach is advocated; that is, each case should be considered on its own merit and the patient and family should be consulted to reach a joint decision about whether prophylactic surgery is worth attempting.

What should we do then when faced with a patient with CMN who attends our clinic? Often, the patients not only ask for prognostic information but also want aesthetic solutions. As for the risk of malignancy, the most recent studies show that the risk of developing melanoma in CMN is low and that regular examination seems a reasonable approach. However, it is not easy to convince a patient (or his or her parents) that CMN covering large areas of body surface are merely an aesthetic problem that does not merit intervention. Some therapeutic approaches such as chemical peeling,[21] laser therapy,[22] and dermabrasion[23] or curettage[24] have been developed and may improve the cosmetic appearance of the nevus without completely eliminating nevus cells. As a result, there is a risk that some residual melanocytes might undergo malignant transformation,

although such procedures may offer considerable aesthetic improvement of the superficial component of the CMN and even reduce the total number of melanocytes with malignant potential.[25] Nevertheless, opinions on this matter also differ. For some dermatologists, these techniques may mask the initial changes of a malignant process whereas others think that elimination of surface cells would facilitate early detection of melanoma.[24] Regardless of the approach taken, and as expressed eloquently by some authors, these individuals will never feel completely normal when they undress in a locker room.[26]

In our professional experience, we have yet to encounter a case of melanoma in a CMN, but we are a pediatric hospital whose patients are lost to follow-up when they become adults, so we do not know whether any of these have developed melanoma later in life. We have however seen some patients who have undergone the operation and the results have been far from satisfactory. In general, our approach is conservative and we do not recommend routine excision of congenital nevi unless clinical criteria make such an operation advisable. We are in agreement with other authors in that each case is different and that we must also bear in mind the concerns of the family, the complications associated with surgery, and aesthetic and functional factors. Unfortunately, the alternative therapies mentioned earlier have not been widely implemented in Spain and so, at present, are not viable options for our patients.

The last word on the best therapeutic approach for CMN has yet to be pronounced. The findings of the systematic review discussed in this article should be revalidated with new studies that allow a homogeneous long-term analysis of a large number of patients, a difficult objective unless multicenter studies involving several specialties are conducted. However, the creation of an online registry of CMN is an excellent and scientifically valid alternative to epidemiologic studies and multicenter observational studies.

Conflicts of Interest

The authors declare no conflicts of interest.

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