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Multiple miliary osteoma cutis: a comprehensive review and update of the literature

Multiple miliary osteoma cutis consists of heterotopic foci of bone tissue in the dermis and subcutaneous tissue. Patients usually present with multiple, asymptomatic facial papules of several millimetres in diameter which cause distress regarding their cosmetic appearance. The condition is described as rare, as only a few cases have been reported since its first description in 1864 by Virchow. We therefore carried out a comprehensive literature search and review, in which 102 published cases were retrieved and analysed. The demographic and clinical aspects, as well as current therapy solutions, of this probably overlooked condition are discussed.

Key words: multiple miliary osteoma cutis, demographic, clinical, treatment

Heterotopic foci of bone tissue in the dermis and subcutaneous tissue are collectively called "osteoma cutis" (OC). Current knowledge divides the condition into its rarer, primary form (15-20%), in which lesions arise *de novo* on healthy skin, and the more common secondary form (80-85%) [1], in which ossification occurs as a metaplastic phenomenon on a pre-existing lesion, derived from inflammatory, neoplastic, metabolic, traumatic, or iatrogenic insults. As described by Virchow [2] in 1864, multiple miliary osteoma cutis (MMOC) is an ambiguous variant of OC as it can encompass both forms, the latter almost always reported as acne sequelae [1, 3, 4]. We recently encountered an uncommon case of primary MMOC in a dark-skinned patient [5], which compelled us to perform a literature review about this rarely documented dermatological condition. Based on the literature, MMOC is claimed to affect women with a history of acne and present with multiple facial papules which cause concern regarding cosmetic appearance. However, we found this to be speculation as the evidence is mostly based on case reports and a few case series and, so far, only a single thorough literature review has been published [6]. Therefore, a larger comprehensive review and update of the literature on this rarely reported condition is necessary.

Methods

A systematic literature search was carried out on the MEDLINE® database using the key word combination "miliary osteomas" OR "osteoma cutis" in English, German, Spanish and Portuguese. To extend this search, references from the reviewed articles were also assessed. The retrieved non-duplicated articles were scrutinised for relevancy. Reports of primary and secondary miliary osteoma cutis were reviewed. Altogether, from January 1926 to June 2017, 73 articles reporting a total of 102 MMOC cases were found and considered of interest [1, 3-74]. The flowchart depicting the screening process is presented in *figure 1*. Retrieved patient demographics and clinical aspects are summarised in *table 1* and analyses are presented in *table 1, 2*.

Epidemiology

Authors regard MMOC as uncommon [22], rare [3, 7, 10, 12, 13], or very rare [14], while a few consider it as a relatively common, but under-recognized, condition [5, 15, 75]. Previous and recent imaging studies support this latter view. Kishi *et al.* [76] performed a dental radiographic study and found skin osteomas in 2.2% (48 of 2,089) subjects, while Shigehara *et al*. [77] reported an incidence of 27.8% (44 of 158) based on a similar X-ray investigation. More recently, Kim *et al.* [75] conducted a retrospective analysis of 1,315 sinus computerized tomography (CT) scans and identified a 42.1% prevalence of facial calcified nodules. It is interesting that these lesions were mostly found on the frontal and maxillary regions, overlapping the preferential distribution of osteomas identified in this review. Although a publication bias cannot be excluded, as no dermatological history taking or observational studies were performed, and other conditions such as dystrophic calcinosis can also lead to opaque, calcified facial lesions based on X-ray studies, the reported imaging evidence appears to support the perspective that MMOC is in fact under-diagnosed [5]. It is probable that most lesions are of subclinical nature, with only the most exuberant cases or those on the more aesthetically-conscious individuals being brought to the attention of the physician. Misdiagnosis and the benign behaviour of the condition may also contribute to under-reporting.

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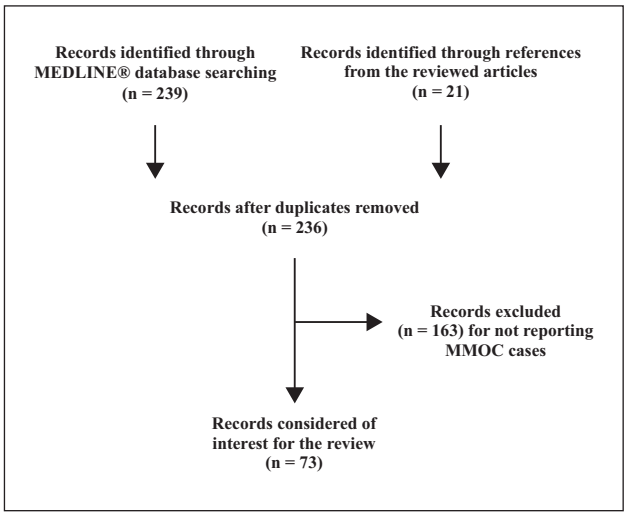

Figure 1. Flowchart of the study selection process.

Pathogenesis

The physiopathology of the disease remains unclear. MMOC is an acquired condition, characterised by abnormal bone formation in the deep dermal or hypodermal skin layers, as proven by the presence of hydroxyapatite crystals on X-ray diffraction [78, 79]. Mesenchymal stem cells, which reside in all postnatal tissues including the skin, are presumably capable of committing to an osteogenic lineage [80]. It is reasonable to believe that abnormal differentiation of these multipotent cells represents the cornerstone of the disease. Progressive osseous heteroplasia, Albright hereditary osteodystrophy, and plate-like osteoma cutis are all primary forms of osteoma cutis that share an identified defective gene (*GNAS*). Fibrodysplasia ossificans progressiva (FOP) is another primary form of osteoma cutis with an identified mutation (within the *ACVR1* gene). These genetic mutations create a sensitized, permissive environment for ectopic ossification. In primary MMOC, a candidate defective gene has not yet been identified [6, 80]. For the secondary form, inflammation induced by an inciting stimulus (trauma or cutaneous conditions, such as acne) is thought to be the initial step for the metaplastic transformation. Subsequent activation of a cytokine cascade and tissue hypoxia are responsible for the recruitment of resident and haematogenic multipotent mesenchymal cells [81], as well as dermal fibroblasts [78]. Skeletogenic-inducing molecules subsequently guide these cells onto an osteoblast-like path [80]. Oestrogens inhibit bone reabsorption, and replacement therapy has protective effects against osteoporosis in oestrogen-deprived states [82, 83]. Since women are disproportionally affected (female-to-male ratio: 8:1; see section on *Clinical manifestations*), a hormonal role in the pathogenesis of the disease has been discussed. This is controversial as both men and postmenopausal women also develop miliary osteomas, albeit less frequently [6]. Moreover, heterotopic ossification on burn wounds is more common in males [84]. The role of hormonal replacement therapy (HRT) has also been discussed, however, based on this review, only seven patients (6.9%) were reported to have undergone this therapy.

Table 1. Epidemiological and clinical features of cases of multiple miliary osteoma cutis (*n*=102).

	No. of patients (%)
Gender (*n*=84)	
Male / Female	9 (11) / 75 (89)
Skin type (*n*=55)	
Fair skin	34 (59.6)
Caucasian	7 (12.3)
Dark skin	1 (1.8)
Asian	6 (10.4)
African-American	1 (1.8)
FS type I, II and III	5 (8.8)
FS type IV	2 (3.5)
FS type V and VI	1 (1.8)
Age at onset (*n*=76)	
Median (range; SD)	51 (16-79; 14.3)
Age at presentation (*n*=80)	
Median (range; SD)	57 (20-79; 12.6)
Symptoms (*n*=102)	
Yes / No	3 (3) / 97 (97)
Location of osteomas (*n*=83)	
Forehead	29 (35)
Cheeks	65 (78.3)
Chin	16 (19.3)
Temples	4 (4.8)
Nose	1 (1.2)
Jaw	1 (1.2)
Thorax	10 (12.1)
Neck	6 (7.23)
Scalp	4 (4.8)
Back	3 (3.6)
Shoulders	2 (2.41)
Upper arms	1 (1.2)
Limited extra-facial	(9.6)
Acne history (*n*=95)	
Yes / Severe	58 (60) / 12 (20.7)
No	39 (40)

SD: standard deviation.

Clinical features

The majority of patients (84 analysed) were women, with a female-to-male ratio slightly above 8:1 (75 and 9 patients, respectively). The median age at onset was 51 (range: 16-79; standard deviation: 14.3; 76 cases were analysed), the median age at presentation was 57 (range: 20-79; standard deviation: 14.23; 80 analysed cases), and the mean time between disease onset and diagnosis was nearly eight years (64 analysed cases).

Skin type, unfortunately, is under-reported (57 cases analysed). Lack of homogeneity in skin type classification was also a concern, as a standardised scale was not used widely. Nevertheless, MMOC appears to affect mostly white individuals, as 80.7% of cases were reported in white patients (combining "fair skin", "Caucasian", and "≤skin type III" classifications in the cases reviewed). We found less than five cases with dark skin. This is an interesting observation, especially considering that Chabra and Obagi documented a history of severe sunburns and/or tanning in six of 11 MMOC patients (55%) [10]. This condition, being uncommon in patients with darker skin types and affecting mostly

Table 2. Summary of topical, systemic, and surgical treatments of cases of multiple miliary osteoma cutis (*n*=69). Each patient frequently underwent more than one treatment, either simultaneously or in sequence.

	No. of patients	Overall response		
	n	Complete *n* (%)	Partial *n* (%)	Failure *n* (%)
Topical				
Topical retinoids	17	8 (47)	3 (17.7)	6 (35.3)
Topical steroids	1	-	-	1 (100)
Topical tetracycline	1	-	-	1 (100)
12% lactic acid lotion	1	-	-	1 (100)
Systemic				
Isotretinoin	4	-	-	4 (100)
Etidronate disodium	2	-	-	2 (100)
Alendronate	2	-	-	2 (100)
Surgical				
Needle incision and ME	19	19 (100)	-	-
Scalpel incision and ME	13	13 (100)	-	-
CO_2 laser incision and ME	6	6 (100)	-	-
Surgical removal (NS)	6	2 (33.3)	4 (66.7)	-
Er.YAG laser and ME	4	4 (100)	-	-
Dermabrasion-Loo-punch-excision	3	3 (100)	-	-
Punch excision	2	2 (100)	-	-
Dermabrasion	2	1 (50)	-	1 (50)
Electrodessication	1	-	-	1 (100)
CO_2 laser ablation	1	-	-	1 (100)
Front lift	1	1 (100)	-	-

SD: standard deviation; ME: manual extraction; NS: not specified; Er: YAG: erbium-doped yttrium aluminium garnet.

sun-exposed facial skin (discussed onwards), might be linked to excessive ultraviolet exposure.

Most patients seek help due to distress regarding cosmetic appearance. Symptomatic cases are rare, as only two patients were reported to complain of itching and one complained of discomfort.

Based on a total of 83 reports, a topographical analysis was possible. The lesions were almost always present on the face, with the cheeks (78.3%) and the forehead (35%) being the most affected. Extra-facial involvement was mostly found on the thorax (12%) and neck (7.2%). Only 9.6% had exclusive extra-facial involvement. With regards to gender, a clear imbalance was identified; while 50% of men had extra-facial disease, only 5.3% of women had this presentation. Other features were the presence of multiple lesions, which exhibited gross symmetry and firmness to touch, as well as diameters that ranged from 1 to 10 mm. Involvement of a single cheek was also reported [10].

An association between MMOC and acne was postulated more than 90 years ago by Hopkins [38]. In this study, a total of 97 cases were analysed, of which 58 (60%) were reported to have a past history of acne. However, primary MMOC is common and 40% of patients do not have a history of acne or any other identifiable causal factors.

A comparison between the mean age at disease onset in the positive (*n*=42) and negative (*n*=32) acne history subgroups was performed (74 patients). No significant relationship could be established, as the mean age at onset was similar in both (46.8 years in the acne subgroup vs. 49.8 years in patients without acne). This finding challenges the assumption that MMOC patients with a history of acne are significantly younger than their primary form counterparts [4, 22].

Laboratory evaluation was abnormal in three reports [7, 18], in which secondary hyperparathyroidism was detected.

Diagnosis

The diagnosis should be suspected clinically and confirmed by a skin biopsy. According to this review (see section on *Clinical features*), the patient is usually a middle-aged, fair-skinned woman with a long-standing history of multiple, slowly enlarging, facial lesions. In men, lesions are often found elsewhere (scalp, neck or trunk). More often than not, a history of acne is identified. Clinical examination shows firm, non-tender, skin-coloured papules and nodules of several millimetres in diameter. It is not uncommon for these lesions to be misdiagnosed (and improperly treated) as adult acne (see section on *Differential diagnosis*), despite the fact that late onset of lesions is not suggestive of adult acne.

Pathology

The histological image of MMOC is usually interesting [5], as it encompasses true bone formation in the dermis; usually on the reticular layer, lamellar bone tissue entrapping osteocytes can be seen surrounding an adipocyte cortex, sometimes with haematopoietic capacity.

Differential diagnosis

MMOC is a frequently misdiagnosed condition, as it mimics other routinely observed dermatoses. Consequently, the

patient undergoes unnecessary treatments because appropriate diagnosis is delayed. Acne, as highlighted by our case [5] and others [9], is the most frequent misdiagnosis, as deep-seated osteomas can be similar in appearance to macro and microcomedones. A recalcitrant nature despite adequate treatment should point towards correct diagnosis. Calcified milia [10], sebaceous hyperplasia [10], basal cell carcinoma [10], warts [17], eccrine hydrocystoma [76], cutaneous sarcoidosis [17], and miliary lupus [17] should also be considered. Ultrasound [13], X-ray [84] or CT [83] may improve diagnostic accuracy, but accessibility, costs, and radiation exposure limit their use.

Treatment

Topical and systemic treatment

Topical retinoids (0.025-0.1%) have been reported to be effective by some authors [19, 21, 25, 26], particularly for the treatment of smaller, superficial lesions [4]. Other reports indicate less satisfactory results [3, 5, 7, 9, 65]. Maximum benefit can take up to nine months [25]. Moritz [19] and Smith [21] reported improvement by means of transepidermal elimination, while Cohen [25] suggested normalisation of fibroblastic differentiation. In theory, retinoid-induced inhibition of chondrogenesis [81] would be of therapeutic interest, but systemic isotretinoin fails to achieve improvement [5, 6]. A study by Goldminz identified a high rate of bone remodelling at the internal surface of osteomas [16]. However, enthusiasm for treatments that block osseous turnover, such as etidronate disodium [16, 17] and alendronate [5, 18], was short-lived, as they failed to achieve any benefit. Moreover, there is an isolated report of facial osteomas developing one year after initiation of alendronate therapy [20].

Surgical treatment

A multitude of techniques have been reported. Small scalpel or needle incisions over the lesion, followed by manual extraction, usually performed with a thin curette, is a simple and successful approach [1, 9, 10, 29, 30, 45, 61]. A skin hook is an alternative to the curette for detachment and extraction of osteomas, and may cause less dermal damage [37]. Dermabrasion was used by Fulton (combined with punch biopsies) [31], Wilhelmsen [33], and Duarte [5] with variable results. A frontlift approach to treat large lesions on the forehead was employed with good outcome by Senti [55]. Baginski [23], Retamar [36], and Kim [75] treated their patients with carbon dioxide (CO_2) laser ablation, and results were satisfactory, aside from the post-treatment hypopigmentation seen in one case. Ochsendorf and Kaufmann [34] successfully used the erbium-doped yttrium aluminium garnet (Er:YAG) laser with a 2-mm spot size to expose the osteomas by precise ablation of the upper skin layers. The authors suggested this laser to be superior to its CO_2 counterpart, as it implies less risk of scarring. Entire facial resurfacing with a 5-mm spot Er:YAG laser was performed by Hughes [35], but this was criticized as total facial exposure and use of a wide spot may lead to avoidable scarring [85, 86]. Prolonged down-time and need for antiviral prophylaxis are also disadvantages [66]. A refined 1-mm spot Er:YAG was later employed successfully by Ortiz [66]. The presented results put in perspective the challenging and controversial treatment for this condition. Moreover, therapeutic modalities were not systematically compared, therefore it is impossible to assess which one offers the best outcomes. On one hand, topical treatments have, in theory, a suboptimal efficacy as the lesions reside deep in the dermis, and current formulations have limited access to these skin layers. Nevertheless, some authors have reported good outcomes with these treatments. On the other hand, the surgical approach offers a better chance of success, and is therefore usually the treatment of choice [10]. However, lesions are multiple, deep-seated, and recurrent, often demanding repeat procedures, thus the dermatological surgeon should be reminded of the unpleasant facial scarring and dyschromia that may follow extensive or deep skin procedures. Treatments should therefore be carefully chosen, and the benefit vs. risk ratio should be assessed individually and discussed with the patient at hand.

Limitations

As a limitation of this review, we acknowledge that the full text of some articles was inaccessible, while insufficient reported data was reported in others, thus making it impossible to establish a complete analysis with statistical correlations. Publication bias should also be considered as data were mostly extracted from case reports and small case series. The high percentage of cases excluded from skin type assessment may have created a bias in this analysis. Nevertheless, this is the most comprehensive review regarding MMOC performed to date, which the authors hope will raise awareness about the condition and insight into its management.

Conclusions

Despite being reported as rare, MMOC is probably a relatively common entity due to its subclinical nature or the fact that it is overlooked, and MMOC is frequently misdiagnosed. Middle age, female gender, a history of acne, and white skin are risk factors. The severity of acne does not appear to increase the risk, and the mean age at disease onset appears to be similar in those with or without acne history. Both findings challenge pre-existing concepts. An association with ultraviolet exposure and sun-seeking behaviours is hypothesized. The facial skin is almost always affected (>90%), and extra-facial involvement is more common in men. Regarding treatment, a large body of evidence favours the simple "incision and curettage" technique, but laser procedures are gaining relevance. Nevertheless, the benefit vs. risk ratio for each treatment should be tailored for and discussed with the patient. Further research to compare different modalities may disclose more meaningful therapeutic recommendations. ■

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