Dear Editors,

the constellation of findings of atrophodermia vermiculata includes irregular elastin aggregates and sweat gland proliferations. It affects a small group of patients and has been described under the disease names Nicolau-Balus syndrome, eccrine follicular hamartoma syndrome, bilateral facial apocrine fibrosing hamartoma, and Rombo syndrome [1–9].

From childhood onwards, affected individuals present with syringoma-like or milia-like lesions and follicular scars on the face, upper trunk, and sometimes extremities [1–3, 6, 8]. Some patients also display unilateral or bilateral infiltrated plaques on the cheeks [8, 9] (Table 1). The latter may be misinterpreted clinically and histologically as microcystic adnexal carcinoma (MAC).

In 2010, Schaller and colleagues first described two patients in whom cheek lesions were initially misdiagnosed both clinically and histopathologically as MAC and were repeatedly and incompletely excised by micrographically controlled surgery [8]. These patients had bilateral plaques on the cheeks that had been present since childhood, as well as facial milia, atrophodermia vermiculata, and syringomas. The patients also had clinical and histopathologic characteristics previously described as Nicolau-Balus syndrome, Rombo syndrome, and by Peyri et al as eccrine follicular hamartoma syndrome [1, 3, 4]. On histologic examination, ductal proliferations were found extending into the deep dermis within a sclerotic stroma [8]. Clinical follow-up, which lasted up to 19 years, revealed no progression of the findings, suggesting benign behavior and hamartomatous character. The condition was therefore termed MAC-like syndrome [8].

The genetic background of these syndromes was not known until now. By genetic analysis of several symptomatic families, pathogenic variants of the MYH9 gene encoding the non-muscle myosin type IIA heavy chain (NMMIIA) have recently been identified. For this purpose, germline exome sequencing of a total of six affected individuals from three families was performed. The MYH9 variants co-segregated with the phenotype and were further sequenced. The variants encoded changes to amino acids that predominantly localized to the ATP-binding pocket and that were otherwise conserved across eight different myosin classes. To emphasize the common genetic etiology, this was described as MALTA syndrome (MYH9-associated elastin aggregation syndrome) [10]. The exact pathogenetic relationship remains to be clarified due to the rarity of the syndromes and the associated low case numbers. One hypothesis is that a signaling cascade important for fibroblast-mediated elastin distribution in the extracellular matrix is altered in patients with the MYH9 mutation [10].

Complementary to the genetic studies [10] we describe the clinical characteristics of one of these families. The index patient, 32 years old at the time of initial consultation, presented with a left-side infraorbital induration of 25 mm diameter (Figure 1). A smaller, approximately 5 mm in diameter, analogous, rough plaque was found over the right zygomatic arch. In addition, there were syringomas on the forehead and cheeks. These had existed since the age of 17 (Figure 2, column 1, line a). An externally analyzed biopsy specimen from the left cheek lesion was found to be MAC. Therefore, micrographically controlled excision and flap plasty was performed in our clinic. Histological examination revealed a vaguely circumscribed dermal proliferation, extending focally to the subcutis, consisting of variably large infundibular cysts and deeper epithelial cell clusters with ductal differentiation (Figure 3). Serial sections also showed no perineural infiltration, so MAC was excluded and a tentative diagnosis of eccrine-follicular hamartoma syndrome was made. Further surgical procedures were not performed. The findings remain unchanged after eight years.

Differential diagnoses include, in addition to the aforementioned syndromes and MAC [11], familial eruptive syringomas [12, 13], plaque-like syringomas [14] and chondroid...
Table 1  Comparison of the cases described with sweat duct proliferations, atrophodermia vermiculata and irregular distribution of elastic fibers.

| Case Description | Age at start | FMH | MAC-like sweat gland proliferations | TE* | Atrophodermia vermiculata | Irregular elastic fibers | Syringomas | BCC | Milia | Hypotrichosis** | Acral cyanosis |
|------------------|--------------|-----|----------------------------------|------|--------------------------|--------------------------|------------|-----|-------|----------------|----------------|
| Nicolau and Balus 1961 (2 cases) Génodermatose polydysplasique | Anamnestic since birth | neg. | Yes, based on histological images | n.d. | yes | yes | n.d. | yes | n.d. | n.d. | n.d. |
| Dupré et al. 1981 (1 case) Syndrome de Nicolau et Balus | Initial examination 10 years | pos. | n.d. | n.d. | yes | yes | n.d. | yes | n.d. | n.d. | n.d. |
| Michaelsson et al. 1981 (12 cases, 2 cases described in more detail) Rombo syndrome Case 1 | 6 years | pos. | n.d. | n.d. | yes | yes | n.d. | yes | yes | yes | yes |
| Case 2 | In childhood | pos. | n.d. | yes | yes | yes | n.d. | yes | yes | yes | n.d. |
| Peyri et al. 1981 (2 cases) Multiple eccrine-follicular hamartomas Case 1 | 2 years | neg. | n.d. | n.d. | n.d. | n.d. | n.d. | yes | yes | yes | n.d. |
| Case 2 | 1 year | neg. | n.d. | n.d. | n.d. | n.d. | n.d. | yes | n.d. | n.d. | n.d. |
| Ashinoff et al. 1993 (1 case) Rombo syndrome | > 3 years | neg. | n.d. | yes | no | n.d. | no | yes | no | yes | no |
| Pujol et al. 1998 (1 case) Multiple follicular hamartomas with sweat gland and sebaceous differentiation, vermiculate atrophoderma, milia, hypotrichosis | 2 years | neg. | n.d. | no | yes | no | no | yes | yes | yes | no |
| Van Steensel et al. 2001 (1 case) A case of Rombo syndrome | 5 years | neg. | n.d. | no | yes | no | n.d. | n.d. | yes | yes | yes |

Continued
### Table 1

| Age at start | FMH | MAC-like sweat gland proliferations | TE* | Atrophodermia vermiculata | Irregular elastic fibers | Syringomas | BCC | Milia | Hypotrichosis** | Acral cyanosis |
|--------------|-----|------------------------------------|-----|--------------------------|-------------------------|------------|-----|-------|----------------|----------------|
| Schaller et al. 2010 (2 cases) Sweat duct proliferation associated with aggregates of elastic tissue and atrophodermia vermiculata Case 1 | 18 years | yes | yes | no | yes | no | yes | no | yes | n.d. | yes |
| Llamas-Velasco et al. 2019 (1 case) Bilateral facial apocrine fibrosing hamartoma mimicking microcystic adnexal carcinoma | 19 years | yes | yes | no | no | no | no | no | yes | no | no |
| Fewings et al., 2019 (13 cases, 5 clinically described) | 8 years | pos. | yes | n.d. | yes | yes | yes | n.d. | n.d. | n.d. | n.d. |
| | 8 years | pos. | yes | n.d. | yes | yes | yes | n.d. | n.d. | n.d. | n.d. |
| | 16 years | pos. | yes | n.d. | yes | yes | yes | n.d. | n.d. | n.d. | n.d. |
| | 6 years | pos. | no | n.d. | yes | yes | n.d. | n.d. | n.d. | n.d. | n.d. |
| | 23 years | pos. | yes | n.d. | yes | yes | no | n.d. | n.d. | n.d. | n.d. |
| Current case, Leipzig 2019 (4 cases, 1 case described in more detail) Bilateral facial sweat gland proliferations and atrophodermia vermiculata | 16 years | yes | yes | no | yes | yes | yes | no | yes | no | no |

Abbr.: BCC, basal cell carcinoma; FMH, family medical history; MAC, microcystic adnexal carcinoma; neg., negative; n.d., not described; pos., positive; TE, trichoepithelioma.

*In some of the cases, desmoplastic trichoepitheliomas have been described instead of MAC-like changes, but these may fit into the histomorphologic spectrum of MAC-like sweat gland proliferations.

**Hypotrichosis of the eyebrows, loss of eyelashes associated with eyelid margin changes with entropion or ectropion.
syringomas [15]. The case of a plaque-like syringoma previously interpreted as MAC has been described [16], as has the case of an eight-year-old female patient with small, nevoid, follicularly bound papules on both thighs. Histologically, the latter was evaluated as sclerosing sweat gland carcinoma or MAC in several biopsies. This patient also showed atrophoderma vermiculata of both cheeks from birth [17].

Typically, MAC is characterized by a solitary, locally aggressive, slowly growing, nodular or plaque-like, skin-colored tumor. In histopathological examination, small horny cysts are found in the superficial portions of the tumor, as well as small collections of pale epithelial cells and syringoid and tubular structures surrounded by a sclerotic stroma extending into the subcutaneous tissue. In deeper areas, (peri)neural invasion is often recognized. Immunohistochemically, there are no specific markers. Therefore, a sufficiently deep biopsy to assess the morphological growth pattern at depth is indispensable for a correct histological diagnosis [11, 18, 19].

In our case, a family medical history and human genetics presentation were conducted after diagnosis. The patient’s brother and sister as well as his father, grandfather and a great uncle were affected by similar skin lesions (Figure 2).

Based on the genetic similarities described by Fewings et al. [10] it can be assumed that the different syndromes represent a common disease spectrum. Genetic analysis of additional affected families may be an important step [10]. From our point of view it is important to raise the awareness for this constellation of findings and this group of rare syndromes with MAC-like sweat gland proliferations, because only in the synopsis of clinic and histology can a MAC be excluded. However, if this is successful, the affected patients are spared unnecessary surgery.

Figure 2 Overview of the clinical pictures of the affected family members, columns: 1: index patient, 2: brother, 3: father, 4: grandfather, rows: a: forehead, b: cheek or forehead with details of the skin lesions in the face, c: upper arm, overview, d: upper arm, detail.

Figure 3 Poorly circumscribed dermal tumor with infundibular cysts and deeper located epithelial cell aggregates with ductal differentiation without cytomorphological abnormalities (hematoxylin-eosin stain, original magnification x 100).

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Conflict of interest
None.

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