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Helen Ollendorff-Curth: A dermatologist's lasting legacy

Introduction

Helen Ollendorff-Curth (Fig. 1) was one of the first female pioneers in academic dermatology and the study of genodermatoses, and her research contributions continue to resonate today. Born in 1899 into a successful Jewish family in Breslau, Germany (now Wroclaw, Poland), she grew up under the guidance of her mother, Paula, a women's advocate in her own right. Paula was an elected city councilor and social advocate who worked to establish supportive housing for single women and victims of domestic abuse (Burgdorf and Hoenig, 2013).

Ollendorff-Curth's early life was not without hardship. She lost her father at a young age and, tragically, only two of her three siblings lived to adulthood. Nevertheless, determined to pursue a career in medicine, Ollendorff-Curth flourished while attending several prestigious German universities, rotating in Breslau, Freiburg, and Munich. This was an extraordinary accomplishment given that she was a Jewish woman, a demographic that was part of an extreme minority in the profession at the time (Burgdorf and Hoenig, 2013; Burgdorf and Scholz, 2004).

When she graduated from medical school in 1923 (Bader and Shipman, 2015), the rise of the Third Reich and the dawn of World War II proved to be pivotal in Ollendorff's career. Growing anti-Semitism in Germany catalyzed her immigration to the United States where she, along with her husband, Rudolf Wilhelm Paul Curth, would form a longstanding professional relationship with Columbia University (Burgdorf and Hoenig, 2013; Burgdorf and Scholz, 2004).

Of particular interest, Ollendorff-Curth lent both her maiden and married names to four distinct eponymous entities still in use in academic dermatology. First, the Ollendorff probe sign refers to the exquisite tenderness of papules found on the palms, plantar surfaces, face, flexural surfaces, and trunk of patients with secondary syphilis when touched gently during an examination probe (James et al., 2011). The probe sign, which helps distinguish syphilitic from non-syphilitic lesions, was originally published as a component of Ollendorff-Curth's medical school thesis, which earned her top honors (Burgdorf and Scholz, 2004). Later in her career and before emigrating from Germany, Ollendorff-Curth—as she was known after her marriage—would further define the "Curth criteria" in her seminal work on acanthosis nigricans for the diagnosis of paraneoplastic dermatoses. The "Curth criteria" were defined as concurrent onset with primary neoplasm, parallel development/resolution with primary neoplasm, specificity between tumor type and cutaneous eruption type, and significant statistical and genetic association between dermatosis and malignancy (Bader and Shipman, 2015; Thiers et al., 2009). During this time, she also provided key insight into the classification of acanthosis nigricans, insisting upon differences in disease course and age of onset between the benign and malignant forms of dermatosis. Benign is often early-onset and genetically-determined, while the malignant form is associated with underlying neoplasm (Curth, 1952).

Ollendorff-Curth also earned the distinction of being eponymously commemorated in two separate genodermatoses: Buschke-Ollendorff Syndrome (BOS) under her maiden name, and Ichthyosis hystrix, Curth-Macklin (IHCM) type under her married name (Burgdorf and Hoenig, 2013). The current article provides an update on these two conditions and shows how modern genetic analysis of affected patients has both improved our understanding of the disease pathophysiology and honored the legacy of one of the first female leaders of academic dermatology.

Buschke-Ollendorff Syndrome

After studying in multiple universities in Germany and earning her medical degree, Ollendorff-Curth moved to Berlin in 1924 and further cultivated her academic career under the tutelage of Abraham Buschke, an internationally renowned professor of dermatology (Burgdorf and Scholz, 2004). Under his mentorship, Ollendorff-Curth first described and defined *disseminated dermatofibrosis lenticularis*, later known as BOS, in 1928 (Burgdorf and Hoenig, 2013; Burgdorf and Scholz, 2004; Woodrow et al., 2001).

BOS is a rare autosomal dominant connective tissue disease, characterized by the formation of elastic and collagenous nevi associated with a spectrum of osseous findings (Woodrow et al., 2001). Dermatologic findings include the development of painless, skin-colored, and often coalescent papules in either an asymmetric or symmetric distribution (Fig. 2). Histological analysis characteristically reveals an increased volume of large, interlacing elastin fibrils (Yadegari et al., 2010). Associated osseous findings vary and typically increase with age. A common associated manifestation is osteopoikilosis, a benign sclerosing bone dysplasia that appears as multiple, well-circumscribed, ovoid opacities seen on plain radiographs of the epiphyses and metaphyses of long bones and the pelvis, and trabeculated small bones of the distal extremities (Fig. 3) (Roberts et al., 1993). These bone islands are small foci of dense remodeled cortical bone with a lamellar structure (Lagier et al., 1984). Some patients may present with melorheostosis, a sclerosing bone dysplasia stemming from abnormal angiogenesis and bone proliferation that characteristically appears as an irregular exophytic cortical hyperostosis resembling dripping candle wax on plain radiography (Fig. 4) (Bansal, 2008). Unlike osteopoikilosis, which is typically an asymptomatic incidental finding, melorheostosis is often painful and may result in severe joint contractures (Gutierrez et al., 2015). Some

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Fig. 1. Helen Ollendorff-Curth. Reprinted from Burgdorf and Scholz (2004), with permission from Elsevier.

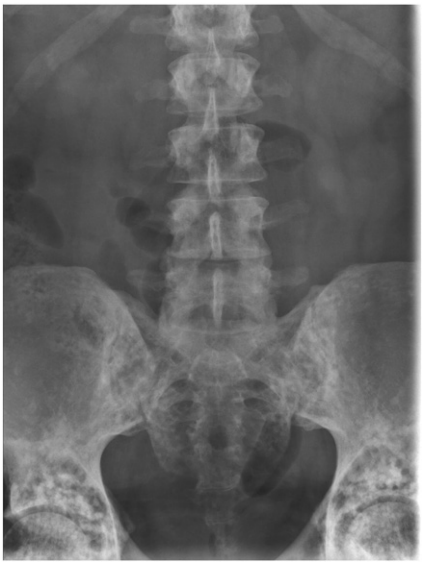

Fig. 3. Osteopoikilosis, a benign sclerosing bone dysplasia, affecting the lumbar spine and pelvis.

authors have reported additional, although less frequent, skeletal manifestations of BOS, including otosclerosis (Pope et al., 2016; Schnur et al., 1994), congenital spinal stenosis (Pope et al., 2016; Schnur et al., 1994), scoliosis (Pope et al., 2016), and craniosynostosis (Reid et al., 2008).

Recent genome-wide linkage analysis studies showed the underlying pathogenesis of the dermatologic and skeletal findings originally described by Ollendorff. BOS is an autosomal dominant disease, described in several series in the literature as recurring in families (Hellemans et al., 2004; Kawamura et al., 2005; Yadegari et al., 2010; Zhang et al., 2009). The causative mutation is believed to be in the gene encoding the LEM domain-containing protein 3 (LEMD3), an inner nuclear membrane protein, which, via interactions through Smad proteins, plays a key role in the regulation of transforming growth factor beta (TGF-β) and bone morphogenic protein (Hellemans et al., 2004; Zhang et al., 2009). Abnormal function of mutant LEMD3 leads to unmitigated TGF-β signaling and consequent increased steady-state levels of elastin messenger RNA (mRNA) and elastin accumulation in the dermis (Woodrow et al., 2001). Of note, increased TGF-β signaling has also been associated with other fibrotic skin disorders (Hellemans et al., 2004; Saito et al., 2001; Mori et al., 2003) and hypertrophic scarring (Korekawa et al., 2012). The skeletal findings in BOS may be directly attributed to loss of LEMD3 function, as increased activity of both bone morphogenic protein and TGF-β have been implicated in increased bone formation in a variety of sclerosing bone disorders (de Vernejoul and Kornak, 2010; Hellemans et al., 2004). To date, 125 pathogenic mutations of the LEMD3 gene have been detected (Kratzsch et al., 2016), which cause the skeletal and dermatologic findings often encountered in BOS through a multitude of different mechanisms, including nonsense-mediated decay of LEMD3 mRNA (Burger et al., 2010) and nonsense-mediated obliteration of the functional domains of the protein (Yuste-Chaves et al., 2011).

In the majority of cases, no specific treatment is indicated because the skin papules are often small and painless (Pope et al., 2016). There is also no significant increase in mortality. However, early and accurate diagnosis of BOS in patients with concomitant elastic nevi and benign osteopoikilosis is paramount in avoiding unnecessary workup and patient anxiety for the incidental discovery of bone islands, which may appear as sclerotic neoplastic disease. Moreover, in patients diagnosed with melorheostosis, active pain

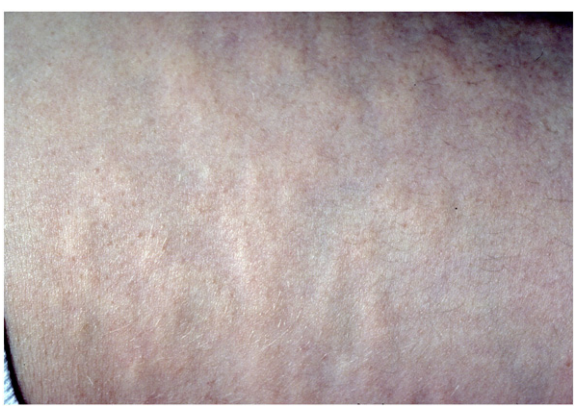

Fig. 2. Painless, skin-colored, coalescent papules characteristic of Buschke-Ollendorff syndrome.

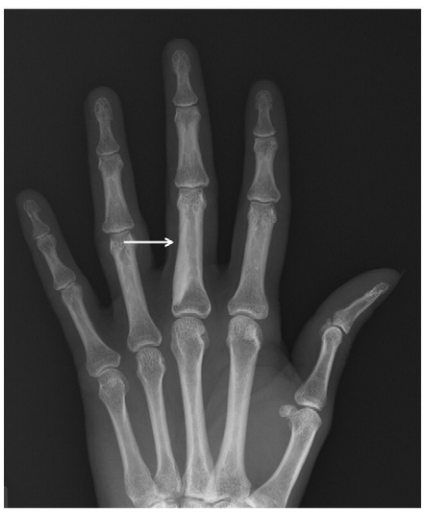

Fig. 4. Melorheostosis involving the ulnar aspect of the third proximal phalanx. Note that it takes on the appearance of dripping candle wax.