A case report demonstrating potential utility of topical imiquimod for cutaneous Rosai–Dorfman disease

Running head: Imiquimod for cutaneous Rosai–Dorfman disease

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Dear Editor,

Rosai–Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy, is a well-defined clinicopathologic entity characterized by nodal involvement and systemic findings such as fever and polyclonal hypergammaglobulinemia (Emile et al., 2016; Brenn et al., 2002). Purely cutaneous RDD is considered a distinct clinical entity that appears to have an older age at onset compared to systemic RDD, with a female predominance (Brenn et al., 2002; Lu et al., 2004). Histopathologically, purely cutaneous RDD is characterized by a mixed inflammatory infiltrate accompanied by S100-positive histiocytes showing emperipolesis. The histiocytes are large and polygonal with abundant palely eosinophilic cytoplasm. Although spontaneous remission has been observed with cutaneous RDD, a subset of patients reportedly have persistent lesions. Therapeutic modalities such as corticosteroids, acitretin, methotrexate, oral thalidomide, dye laser, radiotherapy, or excision were used with variable success for such cases, however, no specific treatment has been established (Brenn et al., 2002; Lu et al., 2004; Mebazaa et al., 2007; Sun et al., 2014; Tjiu et al., 2003). Herein, we describe our favourable experience with topical imiquimod in a patient with cutaneous RDD, and briefly review the possible underlying mechanisms.

A 51-year-old female patient without systemic complaints presented with an 8-month-history of slowly-expanding lesions on the arm and thigh resistant to potent topical corticosteroids. Physical examination revealed two brownish plaques with superimposed clusters of agminated erythematous to violaceous papules and papulonodules located on the anteromedial aspects of the left thigh and left arm (Fig. 1a, d). Skin biopsy demonstrated a highly cellular histiocytic infiltration in the papillary and reticular dermis, with seldom multinucleated cells interspersed among. The histiocytic infiltration was accompanied by a mixed cellular population composed of macrophages, plasma cells, and lymphocytes. On

immunophenotyping, the histiocytic cells expressed S100, but were negative for CD1a and Langerin (Fig. 2). Emperipolesis, the presence of inflammatory cells within the histiocytes, was a prominent finding, consistent with the diagnosis of RDD. Extensive workup with imaging and laboratory studies failed to reveal any signs of systemic involvement, and based on these findings, a purely cutaneous RDD was diagnosed. The patient refused surgical excision and systemic agents like corticosteroids and thalidomide. Based on the immunomodulatory properties of imiquimod (Sauder, D. N., 2000; Schön & Schön, 2007; Wagner et al., 1999; De Meyer et al., 2012), topical imiquimod treatment was planned. After informed consent, treatment was initiated using 5% topical imiquimod cream once daily, every other day. The lesions were noted to gradually flatten and lose their infiltrated nature and erythematous hue. After three months, treatment frequency was reduced to twice weekly, and imiquimod was stopped at the six-month follow-up as stabilization was observed (Fig. 1b, e). During the entire treatment interval, the patient only described mild skin irritation at the application site as an adverse effect. At the final visit six months later, the remaining lesions were further flattened and less prominent (Fig. 1c, f). The patient continues to be in longitudinal follow-up for local recurrence and signs of systemic involvement.

To the best of our knowledge, this case study represents the second report of application of topical imiquimod for the treatment of RDD. Of note, topical imiquimod was used within the context of *in situ* photoimmunotherapy, i.e., in combination with laser irradiation, in the first reported case (Li et al., 2017). We acknowledge the possible role of spontaneous remission, which has been well-documented in some patients with cutaneous RDD, in the aforementioned lesional improvement in our case. However, given the lack of self-healing in the relatively long period before the treatment, spontaneous remission seems less likely to be a major contributing factor.

Imiquimod is a complex immune response modifier, the effects of which are primarily mediated via agonistic activity towards toll-like receptor 7 (TLR7) (Schön & Schön, 2007). Several mechanisms may be postulated to have played a role in the tentative therapeutic activity of imiquimod in our patient. First, imiquimod is known to stimulate both the innate and acquired immune response through induction of cytokines (Sauder, D. N., 2000; Schön & Schön, 2007; Wagner et al., 1999; De Meyer et al., 2012), which may contribute to a therapeutic effect. In addition, proapoptotic activity of imiquimod is well-documented (Sauder, D. N., 2000). Furthermore, an experimental study showed TLR7 expression in macrophages and demonstrated in vitro, that imiquimod was able to induce autophagic cell death in macrophages via excessive stimulation of TLR7 (De Meyer et al., 2012). Of note, anecdotal reports successfully employed topical imiquimod in the treatment of Langerhans cell histiocytosis (LCH) (Taverna et al., 2006; O'Kane, Jenkinson & Carson, 2009; Dodd & Hook, 2016). According to the most recent classification of histiocytoses, LCH and RDD belong to different disease groups ("L" and "R" group, respectively) (Emile et al., 2016). However, both entities are thought to originate from the cells of the mononuclear phagocyte system, and thus, may similarly be susceptible to the therapeutic effect of imiquimod.

Interestingly, gradual improvement was observed while the patient was followed-up after discontinuation of imiquimod treatment. We hypothesize that this sustained improvement may be attributable to a possible "memory" effect on a cellular level, where the inflammatory mediators responsible for disease pathogenesis continue to be under the influence of imiquimod treatment, although this observation and explanation need to be further corroborated.

This case study is limited to a single patient, and the lesions did not undergo complete resolution. Nevertheless, imiquimod treatment was satisfactory from both the patient's and physician's perspective, and spared our patient the side effects of systemic treatment and the

burden of extensive surgery. Imiquimod may be a promising tool in the dermatologist's armamentarium for cutaneous RDD and possibly other cutaneous histiocytoses, which need to be further studied.

Figure Legends

Figure 1. Brownish plaques with superimposed papules and papulonodules located on the anteromedial aspect of the left thigh and arm before treatment **(a and d, respectively)**, at the six-month follow-up of imiquimod treatment **(b and e, respectively)**, and six months following discontinuation of imiquimod treatment **(c and f, respectively)**.

Figure 2. a: Heavy infiltrate occupying entire dermis (Hematoxylin-Eosin [HE] x100); **b:** Clustered plasma cells and lymphocytes accompany the histiocytic infiltration. Cytoplasms are sometimes xanthomatous (HE x200); **c:** Higher magnification where a few phagocytized neutrophils are noticeable (HE x400); **d:** Many histiocytic cells express S100 protein (Anti-S100 x100).

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