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Short communication

Natalizumab induced cutaneous sarcoidosis-like reaction

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ABSTRACT

We present a case of a drug-induced sarcoidosis -like reaction (DISR) occurring following initiation of Natalizumab for multiple sclerosis. The reaction was purely cutaneous, and disappeared following drug withdrawal. We highlight this case to the practicing neurologists, with warning to be wary of a new rash on immunomodulatory therapies.

Natalizumab is a monoclonal antibody, licensed in the treatment of multiple sclerosis (MS). It is also used extensively in inflammatory bowel disease, an entity encompassing granulomata. It is a selective adhesion molecule, specifically acting on $\alpha_4\beta_1$-integrin (Hutchinson, 2007). A decade into common use, Natalizumab remains very popular, although not without side effects. We describe a case report of a 41 year old lady who developed a cutaneous sarcoidosis-like reaction following initiation of Natalizumab.

Our patient presented in September 2017 with left sided abdominal and thigh paraesthesia. She objectively had reduced sensation to temperature, pain and fine touch covering her left lower abdominal quadrant, left hip and left thigh. Her MRI brain was consistent with demyelination, fulfilling criteria for dissemination in space but not time. She had a heavy burden of spinal cord disease to account for her symptomatology. Her oligoclonal bands were positive, fulfilling dissemination in time criteria for the formal diagnosis of multiple sclerosis per McDonald's Criteria (Thompson et al., 2018). Visual evoked potentials showed prolonged latencies bilaterally. Serial imaging 3 months later showed new plaque formation.

She commenced Natalizumab in January 2018, and had four uncomplicated monthly doses. We note that she was JC virus antibody positive, but made a fully informed decision to commence with this treatment. Following the fourth dose, she insidiously developed a non-pruritic annular rash, covering both limbs, and scattered over her torso also (Fig. 1). This was poorly responsive to topical glucocorticoids, commenced by her general practitioner. Biopsy was consistent with a granulomatous dermatitis suggestive of sarcoidosis (Fig. 2). Her serum ACE was within normal limits.

With consultation from our dermatology colleagues, the Natalizumab was discontinued. She has had a normal CT thorax and pulmonary function tests. Her rash has thankfully slowly subsided over a period of approximately 8 weeks, adding weight to our theory that this was a drug-related reaction. Unfortunately, repeat imaging following 6 months off disease modifying therapy showed active enhancement of a T4 lesion. She has since commenced Cladribine, with no interval clinical relapses in the time to submission (5 months).

Sarcoidosis is a multi-systemic inflammatory condition. It is histopathologically characterised by non-caseating granulomatous inflammation. It was initially described in 1899 by a Norwegian dermatologist, Caesar Boeck (1899). A granuloma is a small collection of inflammatory cells, usually occurring as a result of non-degradable antigen with cell-mediated hypersensitivity (Parisinos et al., 2011).

The pathogenesis of sarcoid is believed to be driven by CD4+ T-cells, which are present in histological samples (Iannuzzi et al., 2007). Various environmental antigens have been postulated as possible triggers which initiate an inflammatory cascade, activating these CD4+ cells into type 1 helper T cells (Th1). These in turn, secrete cytokines

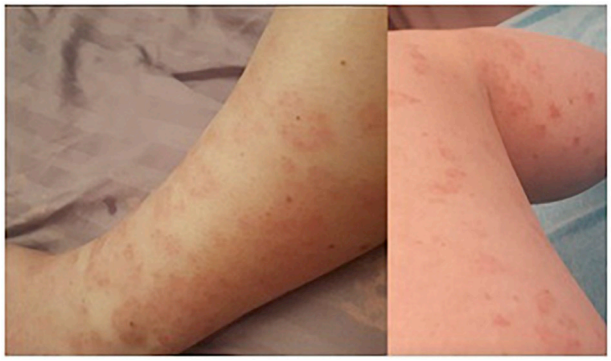

Fig. 1. Images of the rash from the patient's own collection, reproduced with consent.

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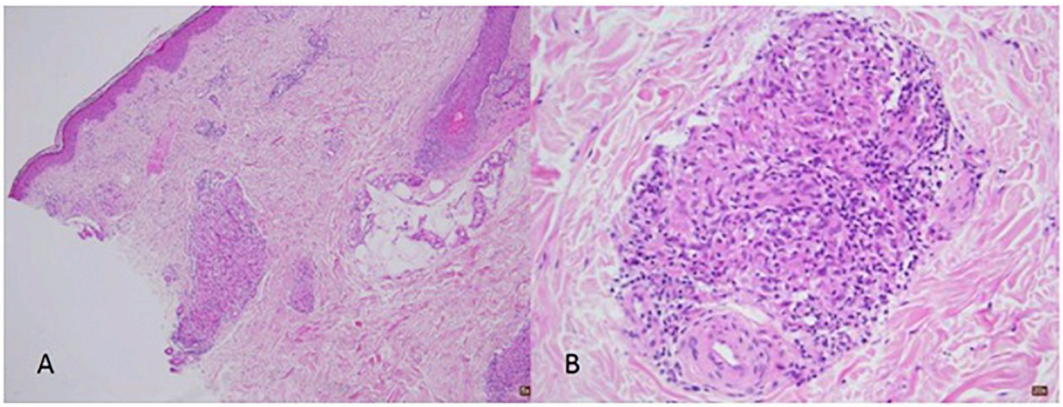

Fig. 2. A) Low power (5×) view of a punch biopsy of skin taken from the rash on her left thigh showing well defined non caseating granulomata within the dermis. B) Higher power (20×) view of a single granuloma which is well formed and is non caseating. Special stains for microorganisms were negative. No significant dermal mucin noted and no vasculitis was evident.

such as interleukin-2 (IL-2), and interferon gamma. This drives a local inflammatory response.

Alongside primary sarcoidosis, lies the differential diagnosis of "Drug-induced sarcoidosis-like reactions". (DISR). These are clinically and histologically indistinguishable from primary sarcoidosis, but have a direct temporal relationship to the initiation of a drug. It remains unclear if this is a different entity altogether, or if it simply represents a clinical presentation of sarcoidosis that begins with initiation of an inflammatory cascade by iatrogenic means. As a possible distinguishing feature, DISR often improves or disappears following removal of the inciting drug, and recurs with repeat drug initiation. It thus may reflect a true drug reaction (Chopra et al., 2018). Common inciting drugs are immune checkpoint inhibitors, TNF alpha inhibitors, interferons and highly active anti-retroviral medications.

Prior to arriving at a diagnosis of DISR, one should exclude other causes of granulomata, aside from sarcoid. The list of causes of granulomata is unfortunately lengthy, and includes infections, vasculitis, immunological upsets, leucocyte oxidase defect, hypersensitivity, chemicals, and neoplasia (James, 2000).

Reports in the literature of DISR occurring with Natalizumab are limited. One such case describes a case occurring in the context of Crohn's disease (Parisinos et al., 2011). We suggest that this case is quite different from ours, as Crohn's is itself characterised by granulomata in many cases. The exact mechanism of the cutaneous reaction which we describe is unclear. As mentioned above, Natalizumab acts on $\alpha_4\beta_1$-integrin. Integrins are heterodimers that are key components in the extracellular matrix. Problems within this matrix have been described in many dermatological conditions (Liu and Leask, 2013). Analysis of sarcoid granulomas has previously demonstrated expression of the $\alpha_4\beta_{1-}$ integrin on surrounding lymphocytes and macrophages (Shigehara et al., 1998). We would postulate that Natalizumab's action at $\alpha_4\beta_{1-}$ integrin may have altered the structural extracellular matrix, inciting an inflammatory cascade with subsequent granulomata formation.

We feel that this case further highlights that the practicing neurologist should be wary of any new rash following commencement of immune-modulatory therapy, such as Natalizumab. Clarifying the timeline of the rash presentation in relation to the infusion schedule is vital, as hypersensitivity reactions have been well described with Natalizumab also (Philips et al., 2006). Dermatological manifestations tend to be urticarial, but systemic anaphylactoid reactions are reported. Delayed hypersensitivity reactions have been shown to occur more commonly in the context of neutralising antibodies to Natalizumab itself, and are more common in the first six months of therapy (Chataway and Miller, 2013).

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