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Title: Neurology and the Histiocytoses: a case of Rosai-Dorfman-Destombes disease.

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Abstract

The histiocytoses are a group of rare disorders characterised by the accumulation of neoplastic or non-neoplastic activated histiocytes in various tissues. Phenotypes vary widely from spontaneously regressing cutaneous lesions or lymphadenopathy to disseminated disease with poor prognosis. Neurological symptoms can occur as a presenting feature, or during the course of disease. We present a challenging diagnostic and management case of Rosai-Dorfman-Destombes disease in a 48-year-old female with a relapsing, partially steroid responsive syndrome comprising patchy, non-length dependent, radiculoneuropathy with diffuse pachymeningitis and widespread systemic disease, and recent dramatic response to novel *MAPK* pathway inhibition. We discuss the clinical characteristics, diagnosis, recent breakthroughs in pathogenesis and emerging treatment options for Rosai-Dorfman disease and the histiocytoses with neurological sequelae including Langerhans Cell Histiocytosis and Erdheim Chester disease.

Case Report

A 49-year-old, right-handed woman presented to her local hospital with a 12-month history of progressive fatigue, night sweats, arthralgia, asymmetric patchy numbness, and distal, upper limb predominant weakness. Examination revealed reduced pinprick of the right face in a V3 distribution, mild weakness of abductor pollicis brevis (APB) and abductor hallucis muscles with brisk reflexes and flexor plantar responses. Pinprick sensation was reduced to the 1st and 2nd digits on the right, 2nd, 3rd and 4th digits on the left and to the ankles bilaterally, with intact vibration and proprioception sensation. Neurophysiology demonstrated motor conduction block of the median nerve in both forearms and an absent F-wave response in the right common peroneal nerve, but otherwise normal motor and sensory nerve function (Supplementary Table 1, 05/2010). The EMG of all tested muscles, including the APB, was normal. Minor degenerative changes were observed on MRI of the neuroaxis. Neurophysiologically, the pattern of findings was thought to most typically reflect multifocal motor neuropathy with conduction block; however, given the predominant sensory symptoms, and likely pre-ganglionic sensory involvement, a presumptive diagnosis of MADSAM was made. A 5-day course of oral steroids resulted in rapid improvement in pain and mild improvements to her neurological symptoms. Figure 1 demonstrates the clinical course, blood parameters, and treatment across the course of the patient's disease.

The sensory symptoms and distal weakness progressed, and she was further investigated 2 months later. The ESR was 75 and CRP was 42, but all other blood tests were within normal limits. The CSF was bland and body imaging with CT was unremarkable (Supplementary Table 2). Neurophysiology revealed worsening conduction block in the median nerves in the forearm with absent F-waves latencies (Supplementary Table 1, 07/2010). Muscle and nerve biopsies were non-diagnostic, specifically revealing neurogenic atrophy, and mild loss of myelinated fibres with acute myelin destruction, thought secondary to axonal degeneration, respectively. Three days of Intravenous methylprednisolone (IVMP) was given followed by a prolonged steroid course with dramatic improvements in pain and

neuropathy symptoms, with return to near baseline function. A steroid taper was performed, with rapid recurrence of symptoms if reduced below 7mg of prednisone.

A year later chin numbness recurred with increased neuropathic pain, upper limb numbness and weakness. She was treated with an induction course of intravenous immunoglobulin with minimal effect. Given the progressive deficits, unclear aetiology and management challenges she was referred for review at a quaternary neurological service.

Examination now demonstrated reduced pinprick of the right face in a V3 distribution, but cranial nerves were otherwise normal. There was bilateral pseudoathetosis of the upper limbs, and asymmetric distal upper and lower limb wasting and weakness, with an MRC sum score of 65/70. Reflexes were now reduced or absent throughout, and plantar responses were flexor. Pinprick was reduced to the wrists and in a superficial peroneal distribution bilaterally, vibration was reduced to the wrist on the right, elbow on the left, ankle on the right, and intact in the left lower limb. Proprioception was reduced to the wrists bilaterally but normal in the lower limbs. Neurophysiology demonstrated diffusely reduced sensory amplitudes and conduction block was observed in the median, ulnar and common peroneal nerves, with small, complex and dispersed compound muscle action potentials and demyelinating range conduction velocities. F-waves were either absent or delayed (Supplementary Table 1, 06/2012). EMG revealed widespread, non-length dependent, neurogenic changes. Further blood investigations were unremarkable (Supplementary Table 2), except for an ESR of 105, CRP of 37 and elevated free kappa and lambda light chains, with a normal ratio.

Serial MRI revealed patchy thickening and enhancement of multiple cranial nerves, nerve roots, the brachial and lumbosacral plexii and discrete peripheral nerves (Figure 2A-D). Of note, thickening and enhancement of the median and ulnar nerves correlated with regions of conduction block identified on neurophysiology (Figure 2D). Dural enhancement over the spinal cord and cauda equina was observed, along with intracranial en-plaque dural thickening and enhancement, prominence of the parotid and lacrimal glands, cervical lymphadenopathy and a presacral soft tissue mass (Figure 2A-C). FDG-PET avidity was seen in cervical, axillary and subpectoral lymph nodes, presacral mass, brachial plexus, bone

marrow and breasts bilaterally (Figure 3A-B). Serial large-volume CSF studies revealed elevated protein with scant lymphocytes but no evidence of malignancy (Supplementary Table 2). A bone marrow biopsy and skeletal survey were unremarkable. Biopsies of an FDG-avid cervical lymph node and the presacral mass revealed a diffuse, paucicellular lymphoplasmacytic infiltrate with clusters of B and T lymphocytes and plasma cells, but minimal atypia or proliferation indices. A presumptive diagnosis of a partially treated, low-grade B-cell Non-Hodgkin's lymphoma, with atypical morphology in the context of previous steroid exposure was made. A further 3-day course of IVMP was given followed by low dose steroids and dexamethasone-cyclophosphamide-rituximab (DRC) chemotherapy was commenced for 8 cycles (Figure 1). Despite symptomatic and functional improvements to near baseline levels (Figure 1), the neurophysiology, MRI and FDG-PET findings persisted.

Prednisolone was subsequently slowly weaned to cessation, with increasing arthralgia and myalgia, but initially stable clinical and investigation parameters, except for a new enhancing left axillary lymph node. Three months after steroid cessation the pain and numbness in the hands, feet, tongue and chin had recurred, with new dysphonia and anosmia, and over the following month progressive distal weakness and sensory ataxia developed. Repeat investigations for a haematological malignancy, including a bone marrow and serial CSF measurements, were negative. FDG-PET and MRI imaging revealed ongoing features as previously described with the suggestion of increased meningeal disease around the pituitary gland. A meningeal biopsy demonstrated numerous histiocytes with admixed plasma cells and small B and T lymphocytes (Figure 4A-F, J-K). The histiocytes were variable in appearance with vacuolation, foamy or eosinophilic cytoplasms (Figure 4B-D), and emperipolesis observed (Figure 2G-I). The histiocytes expressed CD68, CD11c and CD163 (Figure 4C inset, G-I) and were negative for CD1a on immunohistochemistry, with a subpopulation showing nuclear and cytoplasmic S100 positivity, with emperipolesis observed in these cells (Figure 4G-I). These findings are consistent with a diagnosis of Rosai-Dorman-Destombes disease.

Steroids were reintroduced with significant clinical improvement; however, again there was recurrence on taper. As a result, treatment with a CNS penetrating chemotherapy regimen of intermediate dose intravenous methotrexate was commenced, again with symptomatic

response (Figure 1). However, subsequently relapses continue with progression on imaging; despite escalation of therapy with rituximab, azathioprine, mycophenolate, etoposide, sirolimus and ongoing steroids (Figure 1). The meningeal biopsy specimen has been sequentially tested for an underlying clonal mutation; however, to date no mutation has been identified in the *BRAF*, *EGFR*, *KRAS* or *NRAS* pathways.

Thirteen years after initial symptom onset, she experienced a deterioration in vision over weeks from baseline visual acuity of right 6/9, left 6/6 to right 6/60 and left 6/6. Colour vision deteriorated on the right to 6/17 on Ishihara testing, and Goldman perimetry (Figure 5, A) demonstrated loss of sensitivity in the superior temporal field of the right eye. Optic Coherence Tomography showed significant thinning of the peripapillary retinal nerve fibre layer temporal to the right optic disc and borderline thinning in a bow-tie pattern around the left optic disc.

Orbital MRI (Figure 6, A) demonstrated increased mass effect on the inferiomedial surface of the right lateral aspect of the optic chiasm, and the cisternal segments were distorted around the suprasellar mass. There was increased T2 signal in the right optic nerve sheath complex within the optic canal with some extension of the enhancing mass into the inferonasal quadrant of the optic canal. The pattern of visual involvement was compatible with this; the right optic nerve was compromised within the optic canal and the chiasmal disease resulted in the field defect. The possibility of decompressive surgery was explored but deemed high risk due to the position of the carotid artery. Despite negative mutational analyses the decision was taken to commence trametinib, an *MAPK/MEK* inhibitor. Astoundingly, visual improvement was noted after two and a half weeks, and at four and a half weeks, the visual acuity in her right eye had improved to 6/12-2, colour vision to 11/17 and there was improvement in her visual field (Figure 5, B). The field improved further after three months (Figure 5, C). Follow up imaging demonstrated improvement in the size and enhancement of disease in the supra- and para-sellar regions, lacrimal glands and orbital apices (Figure 6, B-C).

Discussion:

The mononuclear-phagocytic system, including dendritic cells, monocytes and macrophages, plays an important role in immunomodulation in health, in particular in presenting antigens to activate naïve T lymphocytes and clearing pathogens and apoptotic cellular debris. Histiocytes are a descriptive term for mononuclear-phagocytic cells when resident in tissues, and histiocytic disorders arise from both clonal and non-clonal proliferation of these histiocytes. The histiocytoses are currently classified by the Histiocyte Society according to their histological, molecular, genetic and phenotypic characteristics[1]. Five categories are described, the Langerhans, cutaneous, malignant, Rosai-Dorfman and haemophagocytic groups. Across these there is marked heterogeneity in the spectrum of disease ranging from benign to malignant, self-limiting to relentlessly progressive, and localised to disseminated[1]. Table 1 outlines the current classification and clinical features of the histiocytic disorders.

The most well-known histiocytic disorder Langerhans histiocytosis (LCH), previously known as Histiocytosis X, is named after the dendritic Langerhans cells, which reside throughout the reticuloendothelial system, but predominate in the skin. Prior classifications differentiated Langerhans from Non-Langerhans histiocytoses, however this distinction has now become more problematic due to the phenotypic and pathological overlap of LCH with other histiocytoses, including Erdheim-Chester disease (ECD) and Rosai-Dorfman-Destombes (RDD) disease, so called “mixed histiocytosis”, and shared mutations of oncogenic pathways[1]. While the dendritic- and macrophage-associated histiocytoses were previously thought to be predominantly due to non-neoplastic proliferation of cells, in the context of infection or inflammation, the recent recognition of common mutations in the mitogen-activated kinase (*MAPK*) pathway, including point mutations in *BRAF*, *MAP2K1*, *ARAF*, *NRAS* and *KRAS*, has indicated a clonal origin of these cells, suggesting these may represent neoplastic conditions. This paradigm shift has dramatically altered ongoing management approaches. In the remainder of this article we will focus upon the clinical manifestations, diagnosis and treatment of RDD disease, highlighting, where relevant, points of differentiation from histiocytoses with neurological manifestations: LCH and ECD.

RDD, was initially described, in the 1960s, by the eponymous authors as “adenitis with lipid excess” and “sinus histiocytosis with massive lymphadenopathy” due to the frequent pathological finding of lymphadenopathy enlarged due to lipid-laden histiocytes. RDD is a rare, relapsing remitting disease, occurring with a prevalence of 1:200000[2]. Reports in differing populations suggest either a male or female predominance, and an average age of 21 to 50 years, with a wide range (2-79 years) of age at symptom onset[2,3]. Classical RDD typically presents with bilateral, painless, cervical lymphadenopathy with associated ‘B-symptoms’; however, extranodal disease is seen in 43-92%[2,3]. Organ involvement commonly involves the skin (10-52%), bone (5-25%), head and neck (11-28%), glandular tissues (breast, lacrimal, parotid; 8-14%), ophthalmic (11%), intrathoracic (2-11%) and abdominal organs (1-14%)[2,3]. Table 2 contrasts the clinical, radiological and histological features of RDD, LCH and ECD.

Nervous system involvement occurs in 5-8% of RDD cases, with rare cases of exclusive CNS disease[4]. Typical manifestations include dural or parenchymal lesions with an intracranial (75%) or spinal (25%) location[2,3]. Dural disease, typically mimics meningiomas, demonstrating a solitary, extra-axial, dural mass with homogenous contrast enhancement on MRI[2]. Parenchymal lesions can occur throughout the CNS, although are commonly infratentorial, particularly involving the brainstem[2]. Patients present with symptoms depending on the location of infiltration, with headaches, seizures, visual, gait, motor or sensory disturbances evolving over weeks to months[2]. Compared to LCH and ECD, hypothalamic-pituitary involvement, neurocognitive and neuropsychiatric features are less well described in RDD[1].

Spinal dural, epidural or expansile bony lesions can lead to spinal canal stenosis or radicular symptoms[3]. As seen in this case, cranial nerve involvement and diffuse pachymeningeal disease has rarely been described[3,6]. To our knowledge, this is the first case of RDD with disseminated plexus and peripheral nerve infiltration (Figure 2B-D), the likely correlate of conduction block seen on neurophysiology (Supplementary Table 1). To date an RDD mass lesion, encasing the medial anteriobrachial cutaneous branch of the ulnar nerve[7], and a child with multiple enhancing cranial and spinal nerves have been described[6]. Of note, similar to this case, the latter was initially diagnosed as variant CIDP after neurophysiology

demonstrated temporal dispersion and conduction block. Furthermore, contrast enhancement was observed in cranio-cervical muscles on MRI, and muscle biopsy showed direct RDD infiltration and demyelination in nerve twigs[6]. It was postulated that the peripheral nerve demyelination may be due to an autoimmune phenomenon associated with S100 autoantibody formation, with cross reactivity to myelinating Schwann cells, astrocytes and glial cells.

The differential diagnosis of this multisystem disease includes tuberculosis, granulomatosis with polyangitis, sarcoidosis, lymphoma, IgG4 disease, carcinomatosis and other histiocytic disorders. Parenchymal lesions may mimic multiple sclerosis, neuromyelitis optica spectrum disorders, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS), sarcoidosis, and lymphoproliferative infiltration, with extra-axial lesions mimicking meningioma. In addition, RDD may be associated with inherited conditions, including germline mutations in *SLC29A3* and *FAS* genes leading to histiocytosis-lymphadenopathy plus syndrome (MIM602782) and autoimmune lymphoproliferative syndrome type 1 (MIM601859) respectively, neoplasia, viral and autoimmune diseases and IgG4-disease[2,3]. As such investigations should be performed to exclude these entities.

Examination of the extent of disease is typically undertaken with whole-body FDG-PET/CT, with RDD lesions found to be FDG-avid, often with an avidity similar to intermediate- or high-grade lymphomas[2]. This can lead to significant diagnostic confusion, as lymphoma is often postulated as the cause of such findings on functional imaging. The distal extremities should be included in PET scanning, with typically more extensive bony avidity seen in lower limb bones in ECD than in RDD[1]. Alternatively, ultrasound, CT or whole-body MRI can be used to identify systemic disease. Symptomatic and asymptomatic neurological involvement is best identified with gadolinium-enhanced MRI of the neuroaxis and additional organ-specific imaging can be required to further evaluate depending on localising symptoms[1]. CSF typically demonstrates elevated protein, with rare occurrences of pleocytosis with emperipolesis seen on cytologic examination[2]. Screening for HIV, hepatitis B and C, parvovirus B19, EBV, HHV-6 is recommended, and have been implicated in the pathogenesis of some cases. Bone marrow biopsies are often required to identify concurrent

haematological malignancy or exclude lymphoma as the aetiology of the multisystem disorder[5]. As in this case, an elevated ESR and polyclonal hypergammaglobulinaemia is observed in up to 90% of patients[4,5]. For our patient the ESR proved particularly useful to monitor disease activity (Figure 1).

In general, however, biopsy of lesional tissue is essential to make the diagnosis. Classically large histiocytes are seen with hypochromatic nuclei, pale cytoplasms and emperipolesis, that is engulfment of erythrocytes, plasma cells or lymphocytes by activated histiocytes (Figure 4G-I). A consistent immunophenotype (S100+, CD68+, CD1a-) is found, and assists to distinguish from ECD and LCH (Table 2). As seen in this case, multiple biopsies are often required to make a diagnosis. In one series a median of 2 biopsies was needed for diagnosis with 18% of cases requiring 3 or more biopsy specimens[3]. Biopsies require fixation in buffered formalin for less than 72hrs to allow histopathology, immunohistochemistry and molecular analyses to be performed[2]. Making a histological diagnosis can often be difficult in RDD due to the rarity of cases and expertise, and the infrequency of typical RDD cells within a pronounced fibrotic and inflammatory background with infiltrates of neutrophils, plasma cells or lymphocytes, and lymphoid follicle formation[2,3]. Flow cytometry and cytogenetic testing is frequently required to exclude haematologic malignancy and IgG4 immunohistochemistry should be performed if the specimen is rich in plasma cells[2]. It is essential that lesional tissue should be assessed for somatic missense mutations generating gain-of function in *MAPK* pathway genes, with 33-50% of patients harbouring mutations in one of *MAP2K1*, *KRAS*, *NRAS*, *ARAF*, *SMAD4*, and less frequently *BRAF*[2,3]. It is suggested that patients harbouring a *MAPK* pathway mutation may have a more aggressive course[3].

Given the rarity and spectrum of this disease, no consistent approach to treatment has been defined, with management options tailored to the individual's disease characteristics. For those with nodal and cutaneous manifestations of RDD, observation may be sufficient, with 20-50% spontaneously remitting[2]. Surgical resection can be curative for unifocal disease and de-bulking can be required for intracranial disease, spinal cord compression, airway obstruction or lesions causing end-organ damage; however, in one series subsequent relapses occur in 33% of cases[2,3]. Radiotherapy has been used for symptomatic or refractory

disease not amenable to surgical resection or as adjuvant treatment for residual intracranial or spinal disease[2].

Corticosteroids are often used as first line therapy, with favourable response in clinical and radiological features seen in up to 56% of cases[2,3]. As seen in this case high doses of prednisone are often required, frequently greater than 0.5mg/kg per day, and relapses are frequent despite prolonged steroid taper (Figure 1)[2]. In disseminated, refractory or relapsing disease systemic therapies are often required. Given the rarity of this condition no prospective trials have been performed for treatment regimens. Case reports describe variable responses to immunomodulation using rituximab, thalidomide, lenalidomide, imatinib, azathioprine and methotrexate[2]. Numerous chemotherapeutic regimens have been trialled, including cladribine, methotrexate, 6-mercaptopurine, vinca alkaloid or cyclophosphamide containing regimens, with high responses rates and sustained remissions seen in some cases[2,3]. Recognition of the dysregulated cytokine and proliferation pathway, mTOR, has led to trials of Sirolimus in RDD and other histiocytoses. In ECD combination treatment of sirolimus and prednisone induced a clinical response and disease stabilisation in 80% of cases and has been used in cases of autoimmune-associated RDD[2]. However, further studies are required to assess for sustained benefit of Sirolimus treatment in RDD.

Considering the recent discovery of *MAPK* pathway mutations in lesional tissues, targeted therapies are now available with the potential to significantly improve outcomes in RDD and other histiocytoses; thus, emphasising the importance of routine testing of lesional tissues for mutations. *MAPK* (cobimetinib, trametinib, binimetinib, selumetinib), *BRAF* (vemurafenib, dabrafenib, encorafenib) and *CSF1R*, *ALK* and *RET* targeted therapies, in development, may be beneficial if lesional tissues harbour the activating mutation. A case report of treatment of *BRAF V600E* positive RDD with darafenib resulted in sustained clinical and radiological improvements[9]. Similarly, *MAPK* inhibition using cobimetinib, in both predominantly pulmonary or gastrointestinal RDD, has resulted in marked and sustained responses in clinical and radiological parameters[10,11]. However, as seen in this case, dramatic improvements may also be observed when mutational analyses are negative. While reported results of target therapies are extremely promising, to date, limited data is available for the response of neurological disease to these therapeutics. This case provides

supportive evidence to suggest that neurological disease may also be responsive to these novel treatments. A prospective trial of cobimetinib in systemic histiocytoses, including RDD, is ongoing.

In light of these molecular advancements, the role of routine, non-targeted immunomodulation is now unclear. Recent consensus guidelines in ECD suggest that non-targeted immunotherapies, surgery or radiotherapy should be used to relieve oedema or acute symptoms but should not be used as long-term monotherapy[8]. Instead, if a specific mutation is identified a therapy targeting that mutation should be the first-line treatment when there is end-organ damage, and in those without an identifiable *BRAF* or *MAPK* mutation an empirical trial of a *MEK* inhibitor should be considered, particularly when there is cardiac or CNS end-organ damage[8]. In those with CNS disease higher doses of *BRA*F or *MEK* inhibitor therapies or dual therapies are recommended to accomplish a marked organ response[8]. However, if targeted therapies are not accessible conventional therapies including interferon-α, cladribine, sirolimus, imatinib, infliximab and methotrexate, can be considered[8]. While these recommendations pertain to ECD, the general principles can be applied to RDD and LCH. Specialist Haematological or equivalent input is essential.

Classical RDD may be self-limited, with excellent outcomes, and prognosis tends to correlate with the number of nodal groups[2]. Similarly, in multisystem disease prognosis correlates with the number of extra-nodal organs involved.[2] Previously, nervous system involvement portends a poor prognosis, with rapidly progressive disability and a potentially fatal course.[2,3] However, due to recent advancements in our understanding of the underlying pathophysiology of the histiocytoses and targeted molecular therapies, prognosis is now markedly improved.

Key-Points:

- Histiocytosis should be considered in the differential diagnosis of multi-system diseases with infiltrative or inflammatory features.
- Detailed phenotyping, clinically, radiologically and biochemically, in a multidisciplinary setting is essential to distinguish histiocytic disorders and differential diagnoses.

- The diagnosis of histiocytic disorders requires one or multiple biopsies with immunophenotyping.
- Assessment of lesional tissue for clonal mutations in *MAPK* pathway is essential to expand treatment opportunities.
- Optimal management requires expert multidisciplinary input and oversight from specialities familiar with histiocytoses and the administration of chemotherapeutic and targeted molecular regimens.

Further reading:

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Figure Legends:

Figure 1: Clinical progress over the course of disease: MRC scores, ESR, and treatments. Abbreviations: IVIg: Intravenous immunoglobulin; DRC: dexamethasone, cyclophosphamide and rituximab; MTX: Methotrexate; AZA: Azathioprine; R: Rituximab; MMF: Mycophenolate mofetil; ETOP: Etoposide: SIROL: Sirolimus

Figure 2 A-D: A: Post gadolinium axial T1w MRI demonstrates pachymeningeal thickening and enhancement along the sphenoid, anterior cranial fossa and tentorium cerebelli (white arrows). Enlarged lacrimal glands (red arrows) are noted. B-C: Coronal post gadolinium fat suppressed T1w images show thickening and enhancement of the brachial and lumbosacral plexii (orange arrows), cauda equina (white arrows), cervical lymphadenopathy (blue arrows) and a large pre-sacral soft tissue mass (yellow arrows) encasing the sacral nerve roots. D: Axial post gadolinium T1w images through the mid left arm shows mild thickening and enhancement of the median and ulnar nerves (blue arrows). Of note conduction block was observed in the median nerve in the mid upper arm segment (Supplementary table 1, 09/2015), correlating with the observed peripheral nerve thickening and enhancement.

Figure 3A-B: FDG-PET CT scans demonstrate diffuse mild FDG-avid uptake in the brachial plexus (orange arrows), bilateral breasts (red arrows), lymph nodes (blue arrows) and the presacral soft tissue mass (yellow arrows). Diffuse but patchy bone marrow uptake was observed with a focal hypermetabolic region noted in the right femur (green arrow). The findings were thought most compatible with a lymphomatous process.

Figure 4: A leptomeningeal biopsy showed a cellular plaque (A) comprising a polymorphic infiltrate of cells, predominantly composed of pleomorphic histiocytes with vesicular and irregular nuclei, and abundant vacuolated (black arrows, B,C) or eosinophilic cytoplasm (D), infiltrating in sheets or nodules amongst proliferating fibroblasts and reactive nodules of epithelial membrane antigen (EMA)-positive meningothelial cells (star and inset, E). Occasional clusters of reactive foamy macrophages (blue arrows, F) were present with accompanying perivascular lymphocytic inflammation (green arrow, F). The histiocytic cells expressed CD68 (inset, C), CD11c and CD163 (not shown) and were strongly immunoreactive for S-100 (nuclear and cytoplasmic, G-I). Frequent emperipolesis was observed (red arrows, G-I). There were accompanying reactive small lymphocytes, predominantly CD3+ T cells (J) with fewer CD20+ B cells (K). The overall morphology and immunophenotype were in keeping with Rosai-Dorfman-Destombes disease.

Figure 5: Visual fields from the right eye (top) and left eye (bottom) in May 2021 (A), June 2021 (B) and September 2021 (C). In May 2021 VA was R 6/60, L 6/6, with colour plates R 6/17 and L 17/17. Due to the poor vision the first field was tested using Goldmann (kinetic) perimetry and demonstrates right upper temporal defect respecting the vertical meridian and a central scotoma, indicating both optic neuropathy and chiasmopathy. Pre-treatment

OCT (not shown) demonstrated established optic atrophy (temporal in the right optic disc and a bow tie pattern in the left). Following treatment in June 2021 (B) there was improvement in vision to the point where Humphrey automated perimetry could be used: this shows mild sensitivity loss in the temporal hemifield of the right eye, and improvement of the central scotoma. There was further improvement in the Humphrey visual field in September 2021 (C).

Figure 6: Post gadolinium T1w (upper row) and T2w (bottom row) coronal MR images. (A) Enhancing T2 hypo-intense dural mass in suprasellar cistern (asterix) with mass effect on the anterior visual pathway. Reduction in mass one month after commencing Trametinib (B) and near-complete resolution of mass effect on visual pathway after three months of treatment (C).

Table 1: Classification and clinical features of the Histiocytic disorders[1]

Group	Subtype	Clinical features
L group: Langerhans	Langerhans cell histiocytosis (LCH)	See Table 2.
	Erdheim Chester disease (ECD)	See Table 2.
	Extracutaneous Juvenile / Disseminated Xanthogranuloma (JXG)	Childhood onset; Phenotype and histopathology similar to ECD (see Table 2); Consider as ECD if activating mutations in MAPK pathway or ALK translocations.
	Mixed Histiocytosis	LCH/ECD.
C group: Cutaneous	**Xanthogranuloma family** - Juvenile Xanthogranuloma (JXG)	First years of life; Benign – spontaneously resolving (months – years), Cutaneous – Yellow to red nodules, solitary- numerous lesions, 0.5-1cm diameter; Extra-cutaneous form – see L group.
	- Adult Xanthogranuloma (AXG)	Adult predominant; Benign –persistent > resolving; Solitary yellow to red nodules.
	- Solitary reticulohistiocytoma (SRH)	Benign – spontaneously resolving (months – years); Typical xanthogranuloma with predominant oncocytic macrophages and ground-glass giant cells on histology.
	- Benign cephalic histiocytosis (BCH)	First 3 years of life; Benign – spontaneously resolving (months – years); Red-yellow papules, limited to head; Overlap with GEH, PNH, papular xanthomas, multiple JXG.
	- Generalised eruptive histiocytosis (GEH)	Adult predominant; Persistent; Numerous flesh-coloured – red macules and papules; develop in crops; Some consider GEH as an initial stage of JXG, XD or PNH.
	- Progressive nodular histiocytosis (PNH)	Rare; Elderly; Spontaneously remitting or persistent; Hundreds of lesions of two types: Superficial xanthomatous papules – nodules, 2-10m diameter and deep larger fibrous nodules; Cutaneous, conjunctival, oral, laryngeal lesions.
	- Xanthoma disseminatum (XD)	Young men; chronic and persistent; mucosal (~50%) and visceral eruptions of disseminated, brown papules and nodules flexor areas and around eyes; Systemic: Diabetes insipidus 40%; FDG-PET increased signal over wrists, knees and ankles.
	Non- Xanthogranuloma family - Cutaneous RDD	RDD deposits localised to skin without systemic manifestations.
	- Necrobiotic Xanthogranuloma (NXG)	Rare; Large, indurated, yellow plaques with telangiectasia, atrophy +/- ulceration; Periorbital and thoracic locations Systemic involvement: Cardiomyopathy, Haematological malignancy; Associations: Paraproteinaemia, MGUS, MM.
	- Multicentric reticulohistiocytosis (MRH)	50-60 y.o. women; Relapsing and remitting; Disseminated cutaneous lesions: papules, nodules or tumours on extremities; Pathognomonic: “coral bead” papules periungual location; Oral or nasal nodules in 50%; Systemic involvement: Destructive polyarthritis; Associations: Malignancy, autoimmune diseases.
M group: Malignant	Primary malignant histiocytoses	Subtypes: histiocytic sarcoma, interdigitating cell sarcoma, Langerhans Cell sarcoma, Indeterminate cell sarcoma; Frequent chromosomal gains or losses; Rapidly progressing tumours of the skin, Lymph node, GIT or CNS; Disseminated disease. Histology: anaplastic tumours with mitotic activity, atypical mitoses, cellular atypia and histiocytic phenotypic markers.
	Secondary malignant histiocytoses	Occurs simultaneously or after a haematologic neoplasm (Follicular lymphoma, Hairy cell leukaemia, CLL, ALL, CMML, LCH) Common immunoglobulin rearrangements, t(14:18) translocation, *BRAF* mutation, chromosomal alteration.
R group: RDD and misc. non-cutaneous non-LCH	Rosai-Dorfman-Destombes disease (RDD)	See discussion and Table 2.
	Histiocytosis not otherwise specified	Cases unable to be classified despite multidisciplinary expert review.
H group: Haemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS)	Primary HLH	Subtypes: Associated with lymphocyte cytotoxic defects, abnormal inflammasome activation, defined Mendelian disorders affecting inflammation or familial (obeying mendelian inheritance) of unknown origin; Rare; First years of life – adulthood; Often fatal; Fever, cytopenia, hepatosplenomegaly, hyperferritinaemia; Often precipitated by infection or vaccination; Haematopoietic stem cell transplant only treatment option, with curative intent; Associations: primary immunodeficiencies.
	Secondary HLH / MAS-HLH	Subtypes: Infection-associated, malignancy-associated (haematological >solid tumours), rheumatological-associated, transplant-associated or HLH of uncertain origin, rare; Occurs in any age group; high mortality; fever, cytopenia, hepatosplenomegaly, hyperferritinaemia.

Table 2: Histiocytoses with neurological symptoms: a comparison of RDD, LDH and ECD[1-3,8]

	Rosai-Dorfman-Destombes disease (RDD)	Langerhans cell histiocytosis (LCH)	Erdheim-Chester disease (ECD)
Age at onset	Classical: Children, young adults Disseminated: 5^{th}-7^{th} decade Wide range (2-79): 8% < 18y.o	Childhood > Adult	5^{th} -6^{th} decades Rare paediatric cases (Range 20-74)
Prevalence/ Incidence	1:200 000 100 case/year (USA)	<15 y.o.: 5-9 x 10^6 >15 y.o.: 1 x 10^6	Unknown; ~800 cases reported in literature
Demographics	Classical /nodal: Males, African descent Cutaneous: Females, Asian descent Disseminated: M:F = 1:1.5, Caucasian descent	M:F = 1:1	M:F = 3:1
Disease Course	Relapsing and remitting; Mild and self-limiting to fatal disseminated.	Self-limiting, pauci-symptomatic to fatal disseminated and progressive.	Self-limiting, pauci-symptomatic to fatal disseminated and progressive.
Neurological manifestations	CNS involvement in up to 8%; Dural lesions – intracranial (75%) and spinal (25%; cervical/thoracic > lumbar) Infiltrative parenchymal disease – infratentorial > supratentorial, periventricular or multifocal Pachymeningeal disease – disseminated Cranial neuropathy – compressive (retro-orbital) or direct infiltration SC compression from paravertebral nodules Peripheral neuropathy or plexopathy – rare, demyelinating neurophysiology.	CNS and pituitary involvement in up to 30%, CNS 2-4% Infiltrative parenchymal disease – hypothalamic-pituitary axis predilection – DI (25%) > hypopituitarism Parenchymal nodular and mass lesions Pachymeningeal disease – nodular thickening of dura, meningioma-like masses Neurodegenerative pattern – demyelination, chronic inflammatory infiltrates, gliosis and atrophy Neuropsychiatric features.	CNS and orbital disease 20-50% Infiltrative parenchymal disease – hypothalamic-pituitary axis predilection (DI (47%) > hypopituitarism), posterior cranial fossa. Parenchymal nodular and mass lesions Pachymeningeal disease – nodular thickening of dura, meningioma-like masses Neurodegenerative pattern – demyelination, chronic inflammatory infiltrates, gliosis and atrophy Orbital disease (25-30%) – compressive cranial neuropathy Neuropsychiatric features CNS disease portends poor prognosis.
Phenotype	Lymphadenopathy (33%), B -symptoms (5%); Generalised (11%), axillary/cervical (8%), thoracic (6%). Cutaneous (10-52%) - subcutaneous nodules, plaques and papules; violaceous or erythematous rash Skeletal (5-25%) - Lytic > sclerotic lesions of metaphyseal heads of femur and humerus, ribs, pelvis, vertebrae; soft tissue extension (6%) Ophthalmic (11%) – orbital soft tissue, eyelid, conjunctiva, cornea, uveitis, sclera Head and neck (11-28%) - trachea, nose, sinuses, vocal cord Glandular (14%) - breast (8%), lacrimal, parotid and salivary gland Kidneys/ adrenal/ retroperitoneum (4%) - Solitary masses, nodules; Less commonly perinephric coating (cf hairy kidney/ECD).	Skeletal (80%) - Osteolytic or osteosclerotic lesions; Axial skeleton, skull, vertebra, innominate bone, ribs Cutaneous (33%) - Macular, popular or nodular lesions, predilection for midline and flexural surfaces Pituitary (25%) - Diabetes insipidus Haematopoietic (15%) Lungs (15%) - peribronchial infiltrates, adults > children Lymph nodes (5-10%).	Skeletal (95%) - Symmetrical cortical osteosclerosis of diaphyseal and metaphyseal regions of long bones Cardiovascular (50%) Retroperitoneal fibrosis (33-65%) - kidneys and ureters “hairy kidney” Cutaneous – Xanthelasma (33%), often eyelid or periorbital Lungs (52%) – lymphangitis, perivascular, pleural infiltrates, pulmonary fibrosis Cardiac – atrial or atrioventricular pseudotumor (37%), periaortic sheathing (62%) “coated aorta” Pituitary – diabetes insipidus Retroorbital disease (27%) - Exophthalmos.

	Lungs (2-11%) – nodules, interstitial pneumonitis, solitary pleural lesions Cardiac (0.1-0.2%)– atrial, aortic infiltration GIT (1-14%)- Liver and spleen infiltration; Colon and rectal polypoid lesions, testicular masses		
Radiology	FDG- PET: FDG-avid cutaneous nodules and masses, lymphadenopathy, lytic osseous lesions; MRI brain- Homogenous enhancing extra-axial lesion (lacks dural tail c.f. meningioma); CT: enhancing orbital infiltration, parotid enlargement, retroperitoneal soft tissue disease	X-ray and CT: Lytic bone lesions CT: Pulmonary nodules and cysts	FDG-PET: bilateral symmetric femur, tibiae and humeri avid-disease – highly specific and useful for monitoring disease activity; CT: "hairy kidney" lesions; micronodular ground-glass opacities and thickening of interlobular pulmonary septa
Histopathology	Multinucleated large histiocytes with hypochromatic nuclei, pale cytoplasm and emperipolesis Florid inflammatory infiltrates with abundant polyclonal plasma cells, activated B cells forming follicles or fibrosis.	Mononucleated cells with coffee-bean or kidney-shaped (grooved) nuclei; Birkbeck granules (X bodies) on EM; Abundant eosinophils and multinucleated giant cells; Mitotic activity may be high, but no nuclear atypia or evidence of rapid progression suggestive of a malignant histiocytosis	Foamy, lipid laden mononucleated histiocytes with small nuclei, and multinucleated histiocytes (touton cells); Background of fibrosis and reactive lymphocytes, plasma cells and neutrophils. Birbeck granules not seen, emperiopolesis may be seen
Immunophenotype	CD1a- CD68+ CD163+ CD207- S100+	CD1a+ CD68+ CD163- CD207+ S100+	CD1a- CD68+ CD163+ CD207- S100-
Predisposing Mutations	Activating mutations in *MAPK* pathway in 33-50% of cases: *N/KRAS* (30%), *MAP2K1* (15-20%), *ARAF* (3%), *BRAFV600E* (3%), *CSF1R* (1%), *CDC73* truncation exon 5	Activating mutations *in MAPK* pathway in >80% of cases*: BRAFV600E* (50-55%), *MAP2K*1 (*MEK1*) (15-19%), *N/KRAS* (2-4%), *ARAF* (1-3%), *ERBB3* (2%), *PIK3C*A (1%), *BRAF* missense (3%), *CSF1R* (1%), *MAP3K1*, *PICK1*, *PICK3R2* Fusions: *BRA*F (3%), *ETV3-NCOA2* (1%)	Activating mutations in *MAPK* pathway in > 80% of cases: *BRAFV600E* (50%), *MAP2K1* (20%), *N/KRAS* (8%), *PIK3CA* (8%; +/- *BRAF V800E*), *ARAF* (4%), *RAF1*, *MAP2K2*, *MAP3K1* In-frame fusions: *BRAF* (2%), *ALK* (3%), *NTRK1* (1%) *ALK* translocations
Associations	ECD 5%, Neoplasia 13% (TCL, MZL, MDS with blasts, WM, MCL), IgG4 related 5%; Immune-related 8% (RA, MS, SLE, Sjogrens, AIHA)	ECD (20%), RDD, Hodgkin's disease, Acute leukaemia, Smoking (Lung LCH)	LCH (20%), RDD

Supplementary Table 1: Serial Neurophysiology

	05/10		07/10		06/12		04/13		07/14		09/15		05/16		04/17		06/18		06/19		01/20	
	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L
Radial uV	45*	49*	39*	41*	11	26	8	13	8	17	2	6	-	6	-	4	-	Abs	Abs	4	Abs	3
m/s					65	64	55	57	64	66	56	66	-	64	-	62				58		53
Median uV	49^	52^	37^	46^	8	3	4	Abs	4	Abs	2	1	-	1	-	Abs	-	Abs	-	-	Abs	Abs
m/s					53	52	58	Abs	54		54	53	-	54	-		-					
Ulnar uV	25^	25^	26 ^	22^	8	7	5	4	4	4	Abs	2	-	1	-	Abs	-	Abs	-	-	Abs	Abs
m/s					59	56	55	51	60	56	Abs	57	-	50	-		-		-	-		
Sural uV	14	12	10	12	Bx	4	Bx	4	Bx	2	Bx	3	Bx	2	Bx	Abs	Bx	Abs	Bx	-	Bx	Abs
m/s						45		43		54		42		48								
Sup. Per. uV	16	13	15	15	8	3	5	5	4	3	3 48	3	-	-	-	Abs	Abs	Abs	-	-	-	Abs
m/s					51	50	44	40	48	51		42	-	-	-				-	-	-	
Median (SE on APB)																						
DML	3.7	4	3.7	3.5	3.1	4.2	4.6	4.5	3.4	3.6	4.3	3.8	-	3.8	-	4.5	-	3.8	4.3	5	4.3	5.2
CV(W-E)	53	50	61	51	45	41	16	39	46	61	38	36		22		27		25	-	30	30	22
CV(E -Ax)	-	-	-	-	47	37	30	16	20	18	21	19		-		-		-	-	-	-	-
CMAP(W)	5.2	5.3	3.3	6.1	2.8	6.2	3	5.4	1.0	3.4	3.4	3.8		3.3		1.3		0.8	0.9	0.8	0.9D	0.2
CMAP(E)	1.9	3.4	1	3	0.6 C	1.2 C	0.9	1.8	0.7D	0.8D	2.3 C	1.9D		2.6		0.7		0.3		0.6	0.5D	0.3
CMAP(Ax)	-	-	-	-	0.5 C	0.6 C	0.4	1.5	07D	0.8D	2.1 C	1.4D		-		-		-		-	-	-
Min F Lat.	30.5	33.8	Abs	Abs	Abs	Abs	Abs	63	Abs	-	Abs	Abs		Abs		46		Abs	Abs	Abs	-	-
Ulnar (SE on ADM)																						
DML	3	3	2.4	2.5	2.7	2.9	3.2	3.6	2.7	3.0	3.3	3.6	-	-	-	4.8	-	-	3.3	4.4	3	4.6
CV(W-BE)	58	55	64	58	57	49	55	53	35	36	33	53				27		28	-	-	31	30
CV(BE-AE	55	60	58	63	40	40	46	35	45	35	23	35				20		33	-	-	28	38
CV(AE-Ax)	-	-	-	-	55	42	55	28	27	-	20	28				-		42	-	-	-	-
CMAP(W)	10	9	7.2	7.3	6.4	6	8.3	8.3	2.3	4.7	3.1	8.3				1.1		0.3	1	0.3	1.1D	0.4D
CMAP(BE)	7.4	6.5	5.6	6.1	4.3	3.8	7.1	6.7	1.5C	2.9C	1.8D	6.7				1.1		0.2	-	0	0.7D	0.4D
CMAP(AE)	6.3	6.7	5	5.9	3.9	3.5	7	6.4	1.3	2.1	1.4D	6.4				0.9		0.4	-	-	0.6D	0.5D
CMAP(Ax)	-	-	-	-	4.3	1.4 C	6.5	3.2	0.7C	-	0.9D	3.2				-		0.2	-	-	-	-
CMAP(Erb's)	-	-	-	-	2.0D	-	-	0.1	-	-	-	0.1				-		-	-	-	-	-
Min F Lat.	25.2	26.1	24.4	30.2	37.5	57.8	35	49	Abs	Abs	Abs	49				Abs		Abs	49	-	-	-
Common Peroneal (SE on EDB)																						
DML	4	4.2	4	3.7	4.1	3.7	5.4	3.7	4.5	4.9	5.3	4.9	-	-	-	-	-	-	6.5	-	-	Abs
CV(A-Fib)	51	49	52	48	42	48	40	48	43	41	34	38							23			
CV(PF –Fib)	53	50	48	47	19	47	17	47	44	-	50	33							25			
CMAP(A)	5.7	5.7	4	5.9	1.8	5.9	0.9	5.9	1.5	1.5	0.3	0.7							0.2			
CMAP(Fib)	4.1	4.7	2.4	3.9	0.8	3.9	0.6	3.9	0.8	0.8	0.2	0.6							0.2			
CMAP(PF)	4.4	5.3	2.7	5.2	0.5 C	5.2	0.7	5.2	0.9	-	0.1	0.6							0.2			
Min F Lat.	Abs	46	Abs	51.6	Abs	51.6	Abs	51.6	-	-	Abs	Abs							-			
Posterior Tibial (SE on AH)																						
DML	4	4.3	3.7	3.6	4.1	-	5.5	3.8	3.3		5.8	3.8	-	3.8	-	Abs	-	-	6.7	Abs	-	Abs
CV (A-PF)	46	46	49	46	-		36	34	-		-	34		34					-			
CMAP(A)	12.5	12.6	13.2	8.8	4.5		8.2	0.1	1.8		4.2	0.1		0.1					0.2			
CMAP (PF)	5.9	7.4	5.8	4	-		2.7	0.1	-		2.1	0.1		0.1					-			
Min F Lat.	49.4	54.8	50.8	67.3	38.9		68	Abs	Abs		78	Abs		Abs					-			

Abbreviations: DML: Distal motor latency, CV: Conduction velocity, CMAP: Compound muscle action potential, W: Wrist, E: Elbow, BE: Below elbow, AE: Above Elbow, Ax: Axilla, Lat.: Latency, A: Ankle, Fib: Fibular head, PF: Popliteal fossa, C: complex, D: dispersed, Abs: Absent, -: Not performed, R: right, L: left. *: antidromic, ^: mixed –palmar responses.

Supplementary Table 2: Investigation results

Serology	
FBC, EUC, LFT, CMP, TFT, iron studies, B12, Folate, MMA, Homocysteine, glucose, HbA1c	Normal
CK	466, 258, 282
ESR/CRP	Chronically elevated (see Figure 1A)
HIV, Hep B, Hep C, Syphilis, Lyme,	Negative
Cryptococcal antigen	Negative
ANA, ENA, dsDNA, ANCA, C3/4	Negative
ACE	Normal -12
IgG/IgA/IgM, EPG, IEPG, urinary BJP	Negative
SFLC	Inc free Kappa 24.4 (ULN 19.4), Free Lambda 37 (ULN 26.3), Ratio 0.66 (N)
LDH	268; 288; 245 (ULN 214)
Cryoglobulins	Negative
Anti-MAG antibodies	Negative
Ganglioside antibodies	Negative
VEGF	1434; 1614; 1365
Endocrine profile	Normal
IgG subclasses	Normal
Tumour markers	Normal
CSF	
2010	Protein 0.33, Glu 3.0 (S 5.4), WCC 1, RBC <1
2012 a (June)	Protein 1.08, Glu 3.1, WCC 4 (lymph), RBC<1, Cytology neg
2012 b (June)	WCC 3, Cytology neg, Flow cytometry neg
2012 c (June)	Protein 1.26, WCC 9 (lymph), RBC <1, OCB matched (CSF>S), Cytology – mild reactive chronic inflammation, without atypia
2013	Protein 0.73, Glu 2.9, WCC 5(Lymph), RBC 40, OCB matched (CSF>S), cytology neg
2014 a (March)	Protein 0.94, Glu 3.3, WCC 6, RBC <1, Viral PCR neg, OCB CSF, Cytology neg
2014 b (July)	Protein 1.3, Glu 2.9 (S4.8), WCC6, ACE N, matched OCB, cytology reactive lymphocytes, flow cytometry neg
Tissue	
Right cervical LN – core bx	Chronic reactive inflammation, no atypia
Bone Marrow 2012/2014	Normocellular, no atypia, MYD88 Neg, cytogenetics neg
Presacral mass – core bx	Diffuse paucicellular lymphoplasmacytic infiltrate with occasional clusters of mixed B, T and plasma cells. No atypia or proliferation – likely chronic inflammatory process

Pre-sacral mass – open Bx	Macro: Fatty brown mass, fused to sacrum; Micro fibroadipose tissue with patchy lymphoplasmacytic infiltration, mixed B and T cells, fat necrosis, no atypia.
Meningeal biopsy	Numerous histiocytes with foamy or eosinophilic cytoplasm, vacuolation and emperipolesis, with admixed plasma cells and small B and T lymphocytes. The histiocytes expressed CD68, CD11c and CD163 on immunohistochemistry, with a subpopulation of S100 positive cells with emperipolesis. NGS: BRAF, EGFR, KRAS. NRAS mutations - Negative.
Imaging	
MRI and FDG-PET	See text; **Figure 2A-B**
CT Chest/Abdomen/Pelvis – 2010	Negative
Mammography, Breast US	Normal
Skeletal survey/ X-rays	Normal
CT Triple phase adrenal	Two Nodules, density 15-19 Hounsfield units, washout <10%, unlikely adenoma, favoured to be RDD nodules.
Functional testing:	
Echocardiogram	Mildly sclerotic aortic valve, mild mitral regurgitation
Angiogram	Left anterior descending artery stenosis requiring percutaneous intervention
Overnight oximetry	Cycling desaturations of variable depth to nadirs 80-90%; consistent with mild obstructive sleep apnoea
EEG	Intermittent right temporal slowing, non-specific, no epileptiform change
Autonomic function tests	Adrenergic and parasympathetic impairment; Cheyne stokes respiration on respiratory traces.
Specialty Reviews:	
Rheumatology	NAD
ENT	NAD
Ophthalmology	2010: NAD, 2020: mild cataracts.