

# Cutaneous Rosai–Dorfman Disease With Linear Lesions and Monoclonal Gammopathy

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**Abstract:** Cutaneous Rosai–Dorfman disease (CRDD), a benign histiocytosis of unknown etiology, typically presents as a solitary or clusters of lesions. Although the histopathology is fairly distinctive, the laboratory abnormalities are not; past reports note elevated erythrocyte sedimentation rate, anemia, and polyclonal hyperglobulinemia. We describe a 61-year-old African American diabetic gentleman who presented with nodules in a linear distribution on the flank. Histopathologic examination of a biopsied nodule revealed a pandermal sheet-like infiltrate of plasma cells and histiocytes, some demonstrating elastophagocytosis and emperipolesis. The lesional histiocytes were S100 and CD68 positive and CD1a negative—findings consistent with a diagnosis of CRDD. Additional laboratory work-up performed 12 weeks after the biopsy was taken revealed an elevated serum  $\kappa$  light chain concentration of 37.26 mg/L (reference range: 3.30–19.40 mg/L), which correlated with an M-protein spike identified as IgG  $\kappa$  proteins per serum protein electrophoresis. Given the difficulty in excising a large area and preexisting diabetes, a course of low-dose methotrexate was selected for therapy with a recommendation of close follow-up for the monoclonal gammopathy. To the best of our knowledge, this is the first report of CRDD associated with a linear distribution of lesions and serum protein electrophoresis-confirmed monoclonal gammopathy.

**Key Words:** Cutaneous Rosai–Dorfman disease, IgG monoclonal gammopathy

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## INTRODUCTION

Cutaneous Rosai–Dorfman disease (CRDD) is a benign histiocytosis of unknown cause first recognized in 2002 as an entity distinct from systemic RDD (SRDD).<sup>1</sup> Since 1969, when SRDD was first described, approximately

600 cases of CRDD have been reported.<sup>2</sup> Patients with CRDD are usually asymptomatic save for nonspecific skin lesions, which can manifest with differing morphologies.<sup>3,4</sup> Laboratory findings with CRDD are nonspecific and can include anemia, elevated erythrocyte sedimentation rate, and polyclonal hyperglobulinemia.<sup>3,4</sup> Herein, we present a case of CRDD with a linear distribution of nodules and an electrophoresis-confirmed monoclonal gammopathy—both of which to the best of our knowledge have not been previously reported.

## CASE REPORT

A 61-year-old African American gentleman presented to clinic with a changing skin lesion on his flank. This lesion began as a solitary nodule excised 1 year before (previous biopsy and report unavailable for review). Shortly after, a crop of lesions appeared around the excision site in a linear distribution. The patient noted discomfort in and around the lesion but denied fevers, chills, night sweats, bone pain, and unintentional weight loss.

The patient had a long history of poorly controlled diabetes, a laminectomy, and a partial cystectomy for a benign bladder mass removed 10 years ago. He quit smoking 6 years ago and denied alcohol or illicit drug use. He had a strong family history for diabetes and heart disease along with colon cancer, which claimed his sister's life.

On physical examination, the left flank had multiple exophytic dermal violaceous to hyperpigmented firm, nontender keloidal nodules in a linear distribution adjacent to an excision scar (Fig. 1).



**FIGURE 1.** Clinical image of linearly distributed nodules.

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The authors declare no conflicts of interest.

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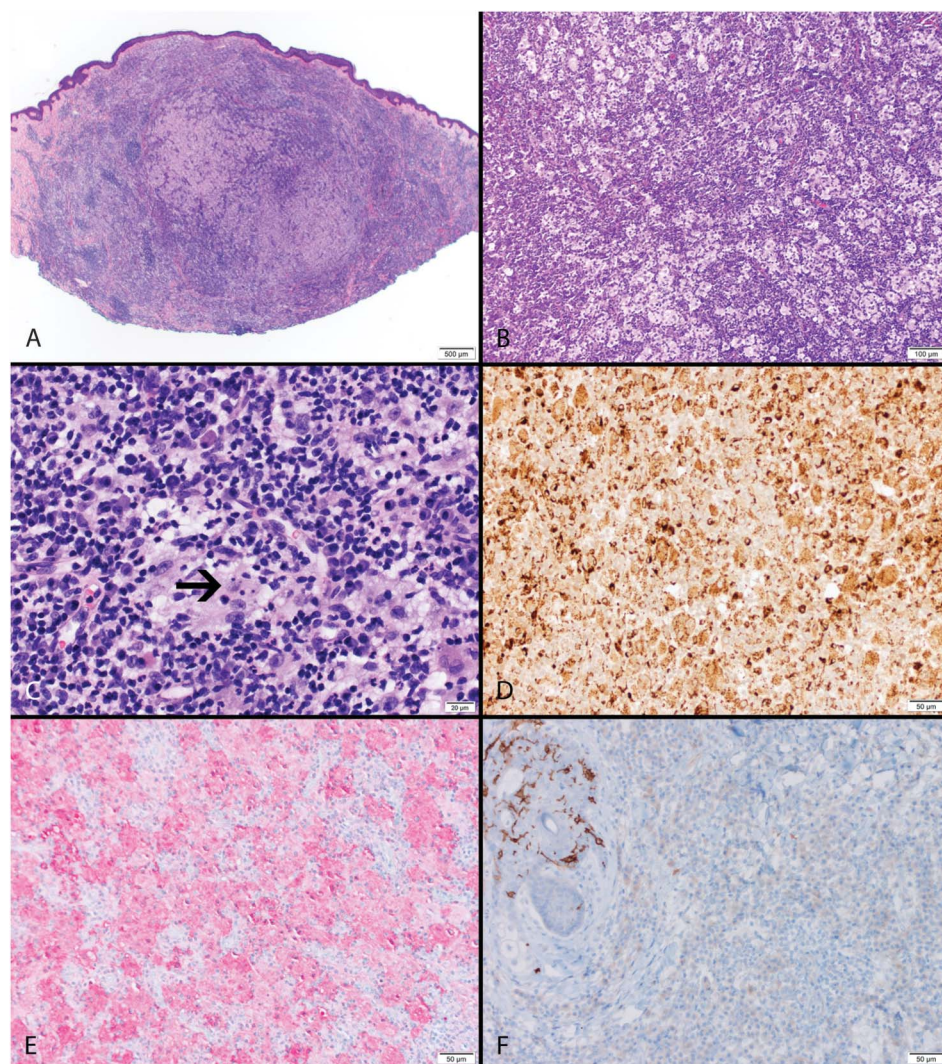
There was no cervical, axillary, or inguinal lymphadenopathy or organomegaly. Vital signs were stable, and he was afebrile. Histopathologic examination of a biopsied nodule revealed pandermal sheet-like infiltrate of plasma cells and histiocytes, some demonstrating elastophagocytosis and emperipolesis (Fig. 2). The lesional histiocytes were S100 and CD68 positive (CD1a negative)—together with emperipolesis, these findings were consistent with CRDD. The lesional plasma cells revealed a slight preponderance of  $\kappa$  compared with  $\lambda$  light chains—which was within normal limits ( $\kappa$ : $\lambda$  ratio of 2–3:1) (Fig. 3).

Laboratory analysis (Table 1) revealed mild normocytic anemia consistent with his baseline, a serum IgG of 1251 mg/dL (reference: 700–1600 mg/dL), and serum protein electrophoresis—confirmed IgG  $\kappa$  monoclonal gammopathy (Table 1). A positron-emission tomography was negative for neoplastic processes. With regard to treatment, given the difficulties in excising a significant portion of the flank and the comorbidity of diabetes, the clinical decision made was to pursue a mild immunosuppressive oral therapy of low-dose methotrexate. An excisional biopsy was performed 2 months later, which revealed histopathologic findings consistent with the initial diagnosis of CRDD.

## DISCUSSION

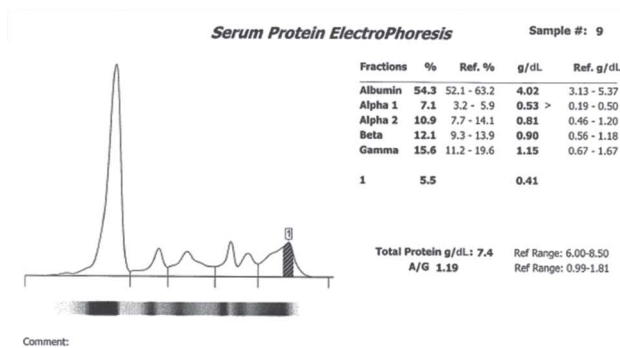
CRDD typically presents with nonspecific skin lesions and no other symptoms.<sup>3</sup> Consequently, one study proposed classifying lesions into 3 types to facilitate recognition of CRDD: papulonodular, indurated, and tumor type.<sup>5</sup> The lesions of our patient most closely resemble the papulonodular type, which is characterized by multiple red or purple nodules growing in a cluster.<sup>5</sup> Of note, nodules growing in a linear distribution have not been previously observed.

The histopathologic differential diagnosis for a polymorphous pandermal infiltrate with lymphocytes, plasma cells, and histiocytes includes benign proliferations, such as generalized eruptive histiocytoma and xanthogranuloma with Langerhans cell histiocytosis being the only entity with malignant potential.<sup>4</sup> The immunophenotype of the lesional histiocytes in CRDD (S100, CD68 positive, and CD1a negative) is useful in differentiating these entities. However, this does not discriminate between CRDD and SRDD. A sign believed to be pathognomonic to SRDD is emperipolesis,



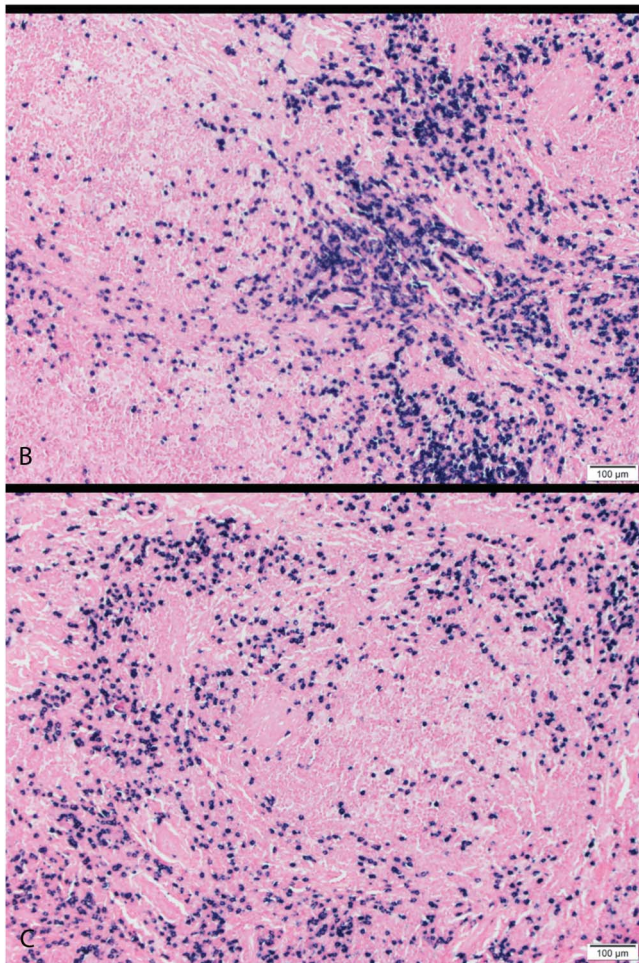
**FIGURE 2.** A–C, Hematoxylin and eosin ( $\times 2$ ,  $\times 10$ ,  $\times 40$ ); arrow in (C) denotes emperipolesis; (D) Immunohistochemistry (IHC), CD68 ( $\times 20$ ); (E) IHC, S100 ( $\times 20$ , red chromogen); (F) IHC, CD1a ( $\times 20$ ).





A

Interpretation:  
PARAPROTEIN IgG KAPPA IDENTIFIED IN GAMMA REGION. This protein occupies 5.5% of the total protein or 0.41g/dL.



**FIGURE 3.** A, Serum protein electrophoresis results. (Note, "1" refers to the spike denoting the IgG  $\kappa$  monoclonal gammopathy); (B) Immunohistochemistry (IHC) on initial biopsy,  $\kappa$  stain; (C) IHC on initial biopsy,  $\lambda$  stain.

a phenomenon wherein phagocytized lymphocytes or plasma cells remain intact in the cytoplasm of the histiocytes.<sup>6</sup> Although this phenomenon is less common in CRDD,<sup>2,7</sup> we observed it in our case.

Laboratory abnormalities typically associated with CRDD are anemia, elevated erythrocyte sedimentation rate, leukocytosis, and polyclonal hyperglobulinemia.<sup>3,4</sup> Of note, our patient exhibited serum protein electrophoresis–confirmed elevated  $\kappa$ : $\lambda$  light chain ratio (Table 1), and monoclonal serum  $\kappa$  light chains nearly double the upper limit of reference range. Thus, we retrospectively performed immunohistochemistry to assess for ratio of light chains in the biopsy, but it was within normal limits with a slight preponderance of  $\kappa$  light chains (Fig. 3).

Monoclonal gammopathy has been observed in select cases of SRDD<sup>3,7–9</sup> but not, to the best of our knowledge, in CRDD (Table 2). Three cases of SRDD with monoclonal gammopathy exhibited an IgA paraproteinemia,<sup>3,7–9</sup> unlike our case which had an IgG paraproteinemia. In one case, a 67-year-old gentleman, with a history of B-cell lymphoma in remission, presented with a swollen testis and found to have an IgA  $\kappa$  paraproteinemia. His right testicle was excised and examined under microscope. Microscopic examination revealed S100-positive histiocytes demonstrating emperipolesis (CD1a was not performed). The patient did not need further therapy and remained disease free since the orchiectomy.<sup>8</sup>

In another case report, a 69-year-old gentleman experienced 30 years of waxing and waning lymphadenopathy associated with SRDD. In addition, extranodal involvement included the parotid gland, skin on the chest, a supraorbital mass, and an epidural mass in the brain complicated by seizures.<sup>7</sup> Pathology of these samples showed sinus expansion with foamy histiocytes and plasma cells more prominent in the noncutaneous specimen.<sup>7</sup> Some of the histiocytes demonstrated emperipolesis, supporting the presumptive diagnosis of SRDD in the absence of immunohistochemical analysis.<sup>7</sup> His laboratory findings were significant for electrophoresis-confirmed monoclonal IgA  $\lambda$  light chain gammopathy.<sup>7</sup> The monoclonal gammopathy remained stable with no evidence of neoplastic processes per skeletal surveys and bone marrow examinations.<sup>7</sup> The patient was treated with chlorambucil and intralesional triamcinolone for his skin, both of which had no effect; his disease was managed with supportive care.<sup>7</sup>

A third case of SRDD with monoclonal gammopathy involved a 7-year-old boy initially presenting with glomerulonephritis and splenomegaly.<sup>9</sup> Approximately 10 years later, laparoscopic splenectomy was performed, during which a large abdominal tumor involving the retroperitoneum, pelvis, mesentery, and omentum was discovered.<sup>9</sup> A year later, laparotomy was performed because of further growth of the abdominal mass and mediastinal adenopathy.<sup>9</sup> Later, he underwent nephrectomy because of recurrent hydronephrosis.<sup>9</sup> Laboratory studies revealed serum IgA  $\lambda$  monoclonal gammopathy (33.67 g/L) concomitant with  $\lambda$  light chains in the urine.<sup>9</sup> Histopathologic examinations of biopsies of the abdominal mass, perinodal soft tissue, mesentery, and tissue from the nephrectomy were consistent with the diagnosis of SRDD. Despite the absence of immunohistochemical data and further in support of this diagnosis was the demonstration of emperipolesis by histiocytes in all tissues microscopically examined. The abdominal mass was not resected, and

**TABLE 1.** Serum Protein Laboratory Investigations\*

| Serum Protein              | Concentration, g/dL | Percentage, % | Reference Concentrations, g/dL | Reference Percentages |
|----------------------------|---------------------|---------------|--------------------------------|-----------------------|
| Total protein              | 7.4                 |               | 6.0–8.5                        |                       |
| Albumin                    | 4.02                | 54.3          | 3.13–5.37                      | 52.1–63.2             |
| Alpha1 globulin            | <b>0.53</b>         | <b>7.1</b>    | 0.19–0.50                      | 3.2–5.9               |
| Alpha2 globulin            | 0.81                | 10.9          | 0.46–1.20                      | 7.7–14.1              |
| Beta globulin              | 0.90                | 12.1          | 0.56–1.18                      | 9.3–13.9              |
| Gamma globulin             | 1.15                | 15.6          | 0.67–1.67                      | 11.2–19.6             |
| A/G ratio                  | 1.19                |               | 0.99–1.81                      |                       |
| M-protein                  | <b>0.41</b>         | <b>5.5</b>    |                                |                       |
| κ Light chains             | <b>37.26</b>        |               | 3.30–19.40                     |                       |
| λ Light chains             | 22.51               |               | 5.71–26.30                     |                       |
| Free κ:λ light chain ratio | <b>1.66</b>         |               | 0.26–1.65                      |                       |

\*The M-protein was identified as an IgG paraproteinemia in the gamma region.

corticosteroids were initiated but stopped after a grand mal seizure.<sup>9</sup> The patient gradually deteriorated and eventually died at 24 years of age after a seizure.<sup>9</sup>

The monoclonal gammopathy and appearance of lesions after excision in our patient raised concerns of progressive disease prompting further testing to guide therapy. A recent report details 3 patients with Erdheim–Chester disease with an immunohistochemical profile of CD68-positive and CD1a-negative histiocytes; in addition to these findings, all 3 cases were positive for BRAF-V600E mutation and had significant systemic involvement. This prompted treatment with vemurafenib leading to rapid

resolution of symptoms within days and regression of disease within 2–3 months.<sup>10</sup> However, there was no evidence of BRAF mutation in our case.

Regarding clinical course, CRDD is largely benign, spontaneously self-resolving in up to 37% of cases with no intervention<sup>2</sup> making treatment contingent upon discomfort or disfigurement. Therapies including antibiotics, cryotherapy, surgical excision, retinoids, chemotherapy, radiotherapy, laser therapy,<sup>2</sup> and thalidomide<sup>4</sup> have been used for CRDD with varying levels of success. Biologics including imatinib have provided relief in SRDD<sup>11</sup> but unfortunately have not met the same success in CRDD.<sup>12</sup> Of the myriad therapeutic options,

**TABLE 2.** Chronologic Literature Overview of RDD Cases With a Monoclonal Gammopathy\*

| Authors                  | Clinical Presentation   | Laboratory Abnormalities   | Histopathology   | Course and Treatment  | Time Free of Disease or Death From Initial Diagnosis   |
|--------------------------|---|--|--|---|--|
| Olsen et al <sup>7</sup> | 69-yr-old black man with a 30-yr history of multiple “histiocytomas” in the brain, parotid gland, supraorbital space, cervical lymph nodes, and skin. | Immunoelectrophoresis—IgA λ light chains<br><br>2.5 g/24 h urine protein—albumin predominant with monoclonal components of IgA λ and free λ light chains<br><br>Monoclonal components have been stable between 2.5 and 3.5 g/dL since 1977 | Lymph node—Expansion of sinuses by atypical histiocytes and plasma cells exhibiting emperipolesis.<br><br>Skin—Infiltrate composed of large histiocytes with foamy granular cytoplasm and plasma cells, although fewer found compared with the lymph nodes<br><br>Prior specimen, including epidural mass, supraorbital mass, and a prior cervical lymph node resection, were consistent with later resected samples, all of which were diagnosed as RDD<br><br>S100 and CD1a staining not performed on any specimen | Patient had a long course of RDD with multiple instances of disease over the course of 30 yrs. In total, 4 cervical lymph nodes, 1 epidural mass, 1 supraorbital mass, 1 mass on left breast were either biopsied or resected. All showed features consistent with the diagnosis of RDD. Chlorambucil 2–4 mg/d did not resolve lymphadenopathy or skin involvement. Intralesional triamcinolone had no effect. His condition was ultimately managed with supportive care. | Despite multiple resections, the patient has continued to experience occasional lymphadenopathy up to the time of writing. |

**TABLE 2.** (Continued) Chronologic Literature Overview of RDD Cases With a Monoclonal Gammopathy\*

| Authors                   | Clinical Presentation   | Laboratory Abnormalities   | Histopathology   | Course and Treatment  | Time Free of Disease or Death From Initial Diagnosis                           |
|---------------------------|---|--|--|---|--|
| Marsh et al <sup>9</sup>  | 7-yr-old white male initially presented with acute glomerulonephritis with notable splenomegaly on examination.   | Serum IgA $\lambda$ monoclonal gammopathy (33.67 g/L)<br>Serum IgG was 10 g/L<br>Serum IgM was 2.7 g/L<br><br>Free $\lambda$ light chains in the urine<br><br>no mention of EP         | Abdominal lymph node biopsy taken during splenectomy revealed histiocytosis with some exhibiting emperipolesis<br><br>Axillary node biopsy taken at 19 yrs of age showed unusual sinus histiocytosis<br><br>Immunohistochemical analysis was not performed on these specimen | 10 yrs after initial presentation, the patient underwent splenectomy, during which a massive midline tumor involving the retroperitoneum, pelvis, mesentery, and omentum was discovered. A year later, the patient had a laparotomy for further growth of the abdominal mass and mediastinal adenopathy. The mass was not resected, and corticosteroids were initiated but stopped shortly after because of a grand mal seizure. The patient gradually deteriorated and suffered anemia, liver failure, bleeding diathesis, and eventually died after a seizure at 24 yrs of age. | Died 7 yrs after initial diagnosis from seizure-related complications          |
| Lossos et al <sup>8</sup> | 67-yr-old male with a history of stage-IV small B-cell lymphocytic lymphoma (in remission for 11 yrs) presented with nontender firm swelling of the right testis. | Elevated erythrocyte sedimentation rate<br>Increased white blood cells counts<br>Monoclonal IgA $\kappa$ paraproteinemia (18 g/L)<br><br>Elevated serum tumor necrosis factor $\alpha$ | Mixed inflammatory cell infiltrate composed of lymphocytes, plasma cells, fibroblasts, and S100 + histiocytes (CD1a not performed)<br><br>Emperipolesis  | A right radical orchiectomy was performed. The anatomical specimen was studied and revealed features consistent with RDD.   | 3 yrs without recurrence or symptoms since right orchiectomy performed in 1994 |

Bolded values indicate that they are present in concentrations above the normal.

\*This table pertains to reports written in the English language.

EP, electrophoresis.

surgical excision remains the most effective with 80% of cases reporting no recurrence.<sup>2</sup> Nevertheless, management of our patient warranted a different approach because monoclonal gammopathy and multiple lesions were potentially signs of progressive disease. Additionally, the lesions inhabited an area too large to resect en masse. Another hurdle was the comorbidity of diabetes eliminating chemotherapy and prednisolone for fear of related complications. Based on these considerations, a regimen of oral low-dose methotrexate was chosen guided by a recent case of a diabetic woman with facial CRDD who experienced complete resolution after a regimen of 15 mg oral methotrexate once per week for 11 months followed by tapering down to 5 mg for 4 more months.<sup>13</sup>

In conclusion, we present the first report of CRDD in a linear distribution with a monoclonal gammopathy. Although the significance of the monoclonal gammopathy is unclear, it

warrants long-term follow-up to definitely exclude systemic involvement.

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