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Langerhans cell hyperplasia from molluscum contagiosum

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Abstract

Langerhans cell histiocytosis (LCH) carries a prognosis which ranges from benign to potentially fatal. There is currently little framework to decipher metrics which predict the benign versus aggressive nature of LCH. We wanted to determine if molluscum contagiosum virus (MCV) DNA could be isolated from a cutaneous lesion demonstrating Langerhans cell hyperplasia resembling LCH in a patient with both. We performed polymerase chain reaction (PCR) on biopsy proven MCV and the hyperplastic lesion. Two specific regions within the MCV genome were detected from both biopsies. We report our findings and suggest that some MCV can produce histologic lesions resembling LCH, similar to the literature on scabies mimicking LCH. Efforts to find a reactive “driver” in LCH may significantly inform the clinical scenario.

Keywords

Langerhans cell histiocytosis; molluscum contagiosum; polymerase chain reaction

CASE REPORT

A 14 year old Caucasian boy initially presented to the pediatric dermatology clinic with 4 umbilicated papules located on his abdomen, right chest and right arm. His past medical history and review of systems was unremarkable. A clinical diagnosis of molluscum contagiosum was made. After discussing the pathophysiology and risks, benefits and alternatives to therapy, treatment was deferred on this initial visit. Six months later the patient returned with a persistent lesion on his lower abdomen. He and his mother report that since his last visit the other papules had resolved and that he had “a few more” develop that had since resolved. This persistent papule was on his lower abdomen and had become pruritic.

Physical examination found a well-developed, healthy appearing young man. He had 2–4mm shallow pockmarks on his chest and arm consistent with resolved molluscum contagiosum. On his right lower abdomen was a 7 mm, erythematous, umbilicated papule. A shave biopsy of this lesion was performed.

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Microscopic examination (Figure 1, A–C) revealed a specimen with a well circumscribed, dense infiltrate of epithelioid cells with reniform nuclei which stained strongly with antibodies against S100 and CD1a (Figure 1, D). These cells did not stain with antibodies against AE1/AE3, EMA or CD68, although there were relatively few scattered CD68 positive histiocytes in the surrounding area. A rare number of eosinophils were found in the sections examined. The epidermis overlying the tumor showed compact parakeratosis with moderate diminution of the granular layer and loss of rete pegs. The diagnosis was consistent with CD1a+ Langerhans cell histiocytosis (LCH). There was no histological evidence of MCV in this specimen on deeper sections.

Upon follow-up for excision of the solitary cutaneous LCH, a new umbilicated papule had formed on his right forearm. The excision on his abdomen of the LCH lesion was performed and a shave biopsy on his right forearm was taken. The biopsy was consistent with molluscum contagiosum (Figure 1, E&F).

Given the almost identical clinical appearance of the lesions and with a concurrent diagnosis of biopsy proven molluscum contagiosum, we decided to perform PCR on all three specimens for molluscum contagiosum virus (MCV) DNA—the initial biopsy of LCH, the excised LCH and the biopsy of molluscum contagiosum. Polymerase chain reaction was performed as previously published¹³ to amplify two distinct portions of the MCV genome. We amplified MCV DNA within both the MCV biopsy, which was expected, as well as from the initial biopsy of LCH (Figure 2A). No bands were detected from the LCH excision specimen.

These are the first results demonstrating MCV DNA within a cutaneous lesion of hyperplastic Langerhans cells which was clinically identical to a molluscum papule and in a patient who concurrently had clinical and histologically confirmed molluscum contagiosum. Our findings suggest, at least in this case, that CD1a+ Langerhans cell collections can be reactive to, or induced by MCV as opposed to intrinsic oncogenic mutations..

MATERIALS AND METHODS

The skin punch biopsy was fixed in 10% neutral-buffered formalin, processed and embedded in paraffin. The paraffin-embedded tissue was cut into 5 um thick sections and stained with hematoxylin and eosin. Immunohistochemistry was performed using the following DAKO LSAB2 kit. Retrieval was performed for EMA, CD68, AE1/AE3, CD1a and S-100 retrieval solution for 20 minutes, followed by peroxidase for 10 minutes. For AE1/AE3 the same retrieval was followed by 50 ul of proteinase K and 450 ul of DI for 6 minutes. Dilution:incubation time were as follows: S100 (1:1000: 20 minutes), CD1a (1:100: 10 minutes), AE1/AE3 (1:50: 10 minutes), EMA (1:50: 30 minutes), and CD68 (1:50: 10 minutes) Antibody for EMA is 30 minutes, S-100, CD68, Cd1a and AE1/AE3 is 10 minutes. Yellow link is then applied for 10 minutes then red link for 10 minutes followed by DAB application.

PCR for molluscum contagiosum virus (MCV) genome was performed with modifications from the protocol by Saral Y. et al¹. In brief, DNA was extracted from formalin fixed

paraffin embedded tissue using a Qiagen DNeasy kit. The following primers were used to amplify MCV genome: F1 (5'-GGCGCGTAGCCGAGCGG-3') and R1 (5'-GCTTCCGGGCTTGCCGCCGGGCAG-3') primers amplify a 393-bp portion of gene encoding p43K; KU (5'-GGAGGAGTGCCCATCAAGAAT-3') and OR (5'-GCTTTTCAGTTTTTGTGCGA-3') primers amplify a 575-bp product from the gene encoding p43K. DNA was amplified and samples were run on a 1.5% agarose gel after 40 cycles. DMSO was used to alter binding properties to allow detection of the 575-bp product in sample X.

DISCUSSION

Reactive or neoplastic; the debate endures regarding Langerhans cell histiocytosis (LCH). LCH is a rare disease consisting of mixed cellularity granulomas containing Langerhans cell-like CD1a+ and CD207+ (langerin+) histiocytes and runs a variable course from benign solitary tumors to fatal multiorgan disease. Historically the definitive diagnosis of LCH was established by the appropriate morphological appearance of histiocytes that had Birbeck granules or stained positively with antibodies for either CD1a or CD207. Yet not all tumors, having met the accepted diagnostic criteria, behave in a consistent, predictable fashion. Thus the debate whether LCH represents a reactive process or true oncogenesis continues to be studied. The clearly benign nature of many cases would favor a reactive process while recent discoveries of specific BRAF mutations in some cases of LCH would favor mutation-driven oncogenic transformation. Bedalian-Very and colleagues identified the oncogenic BRAF V600E mutation in 35 of the 61 LCH tumors they sampled which would suggest true neoplasia, at least in some cases². But how do these "epidermal-resident" CD207+ Langerhans cells (LC) cause multiorgan disease? Via cell-specific gene expression studies it has been proposed that pathological LC in LCH derive from bone marrow derived myeloid dendritic cell precursors and migrate to sites of LCH suggesting CD207 (langerin) is inducible from a bone-marrow source³. Other analyses of LCH being associated with viral infections, such as Epstein Barr virus, cytomegalovirus and other human herpes viruses have borne out mixed results⁴⁻⁷. Supporting a potential reactive etiology for LCH, numerous cases of benign Langerhans cell hyperplasia have been reported with scabies infestation⁸⁻¹⁰. Distinguishing between reactive versus intrinsic neoplastic mechanisms is important as the first scenario is self-limited in contrast to the latter which has a relatively poor prognosis and requires systemic chemotherapy. Although there are no reported cases of LCH associated with molluscum contagiosum to date, we found three case reports of patients with molluscum-like papules ultimately diagnosed as having LCH¹¹⁻¹³. We report our findings in a patient with concurrent solitary cutaneous hyperplasia of Langerhans cells and molluscum confirmed clinically, histologically and by polymerase chain reaction (PCR). We identified molluscum contagiosum virus DNA in the lesion of LCH but not adjacent healthy skin from excision Burow triangles. This effort to find a reactive driver using the more sensitive PCR technique supports a reactive and benign course in the absence of other histological evidence.

Similar reports of Langerhans cell hyperplasia, histologically identical to Langerhans cell histiocytosis, are well established for scabies. We propose that similar findings of Langerhans cell hyperplasia, indistinguishable from LCH, may occur secondary to

mollusum contagiosum. Similarly, clinical lesions of LCH have been reported to resemble mollusum.

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Figure 1.

Biopsy specimens from two clinically similar lesions in a patient with molluscum contagiosum and LCH. An umbilicated papule biopsied on the lower abdomen (A–C at 10×, 20× and 40× magnification, respectively) demonstrates a proliferation of Langerhans cells which stained positive for CD1a (D). Another umbilicated papule biopsied on the right forearm (E & F) shows classic molluscum contagiosum findings with Henderson-Patterson bodies.

Figure 2.

The presence and potential role of MCV in LCH. (A) PCR amplification of MCV in the presence of DMSO free and 1% DMSO buffer. DNA was harvested from 3 different samples. "A" was taken from the right forearm, biopsy consistent with Molluscum contagiosum. "B" was taken from the lower abdomen, re-excision of biopsy site. "C" was taken from the lower abdomen, biopsy consistent with Langerhans cell histiocytosis or hyperplasia. Two different primer pairs, ku+or (a) and f1+f2 (b), were used to amplify two distinct portions of the MCV genome. The sizes of the expected fragments are 393bp and

575bp. DMSO was added to allow detection of MCV from the lower abdomen biopsy. (B) Model of Langerhans cell proliferation driven by MCV infection. In our case, a papule clinically consistent with molluscum contagiosum (clinical photo of patient shown) was histologically striking for expansion of Langerhans cells.

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