Author’s response to reviews

Title: The various clinical spectra of juvenile xanthogranuloma: Imaging for two case reports and review of the literature

Authors:

Michaela Höck (michaela.hoeck@i-med.ac.at)
Bernhard Zelger (bernhard.zelger@tirol-kliniken.at)
Gisela Schweigmann (gisela.schweigmann@tirol-kliniken.at)
Barbara Brunner (barbara.brunner@tirol-kliniken.at)
Bettina Zelger (Bettina.zelger@i-med.ac.at)
Gabriele Kropshofer (gabriele.kropshofer@tirol-kliniken.at)
Ursula Kiechl-Kohlendorfer (Ursula.kohlendorfer@i-med.ac.at)

Version: 1 Date: 03 Mar 2019

Author’s response to reviews:

Thank you for your valuable suggestions, all of which have been considered in the revised manuscript.

In the marked up version of the revision the changes are highlighted in bold. We hope that the manuscript is now potentially suitable for publication in BMC Pediatrics.

Reviewer 1: Bernard Cohen, MD

1. I read with interest the 2 cases, and agree that this should be of interest to the pediatric community. However, symptomatic visceral xanthogranulomas are rare, and general pediatricians are not likely to ever see this disorder.

Commentary:

The aim of our case presentations was to illustrate the various spectra of JXG and make general paediatricians aware of this entity in the interest of making an early diagnosis and prompt adequate therapy, because they are often the first to see these patients. The mother of Patient 2 sought out the general paediatrician due to a recently developed mass on the left temple. He realized, that it could be something serious and referred the girl to hospital for diagnostic work-
up. After admission the patient rapidly deteriorated with paraplegia, so that a delayed diagnosis in this case could have ended fatally for the little girl. Because of the low, but potentially serious risk of internal organ involvement it is pivotal that all paediatricians know signs and symptoms of this rare disease.

Done as suggested: L105, 106 and L 329-331

2. On the contrary, although you note that JXG’s are rare, I actually think that they are underrecognized and underreported. Several pediatric derm text books and studies suggest this as well. I suspect that they are also underreported in dark pigmented individuals, since they are often brown in color in this setting, and since they resolve without treatment, are underdiagnosed.

Commentary:

The real incidence of JXG is unknown, but it may be higher than is generally anticipated because JXGs occur early in life, often as solitary lesions regressing within several years, and are often mistaken for innocent ‘moles’. JXG may affect all ethnicities, but few black patients with JXG have been reported in the literature, probably because they are underdiagnosed and not because Caucasians are more often affected.

Thank you for your suggestions, we agree and incorporated your thoughts in our manuscript: L32-34 and L38, 39

3. Pediatricians should know about the association with cafe au lait macules, neurofibromatosis, and chronic myelogenous leukemia.

Commentary:

Of course, paediatricians should be aware of the triple association of JXG, NF1 and JMML, which is often reported but the subject of frequent debate. In 2004 Burgdorf and Zelger analysed the literature and all available information pertaining to the association and found that patients with NF1 are, indeed, at an increased risk for developing JMML and JXG, but that the triple association of these findings (assuming the worst odds) is < 1% per year. However, regardless of the presence of JXG, children with NF1 are at a 200 to 500-fold greater risk for this hematologic malignancy. Difficulties with regard to these rare events arise as lesions of JXG and NF1 may sometimes be clinically very similar and difficult to differentiate without histology. Moreover, JXG lesions and skin infiltrates of JMML may sometimes also be difficult to differentiate, clinically as well as histologically, all of which has significant influence on these statistical considerations.
Done as suggested: L 43-55, Ref 9

4. You should also take a look at a paper in Pediatric Dermatology 2018;35:582-587 titled Congenital type juvenile xanthogranulomas: A case series and review of literature.

Commentary:

The mentioned review offers a good overview of congenital JXG cases, which are frequently misdiagnosed due to their varied clinical morphologies.

Done as suggested: L 37,38, Ref 6

5. Also had a quick question re possibly getting an alk1 immunostain on the biopsies since this was described as a possible marker for systemic involvement with xanthogranulomas. See Blood, 2006 for discussion.

Done as suggested: ALK immunostaining was performed in both cases, and was negative in both. Thus, we could not confirm the previous study suggesting that ALK might be a marker for systemic involvement.

L 256-261, Ref 36

Reviewer 2: NEUSA YURIKO SAKAI Neusa 626227 Valente

If proved without doubts that the two cases are of juvenile xanthogranuloma (JXG), they are clinically atypical and very interesting, but I am not sure about the diagnoses. When the JXG presents with clinical typical lesions, no histopathology is necessary, but on the contrary, like in these cases, carefull histopathology and immunohistochemistry is essential to confirm the diagnosis and to exclude the differential diagnosis:

1. In the case 1, presenting as blueberry muffin baby, remember that myeloid sarcoma has also this presentation and be positive to CD 163, as in this case. The histopathological figures, without high magnifications do not exclude myeloid sarcoma.

Commentary:

The blueberry muffin-type rash in a neonate is a potentially life-threatening condition with severe sequelae and requires extensive and prompt differential diagnostic work-up. Isolated
myelosarcoma of skin in childhood is a rare manifestation of acute myeloid leukaemia preceding bone marrow involvement by weeks to months. Rare case reports are reported in the literature, where the clinical presentation is described as blueberry muffin spots or symptoms of infection and anaemia. Histologically, most cases were classified as monoblastic or myelomonocytic leukaemia with atypical mitosis. Immunohistochemically, CD43 and lysozyme stained a large proportion of neoplastic cells, MPO and CD117 being the most sensitive of markers for myeloid differentiation, while monocytic precursors consistently strongly expressed CD68 and CD163. Due to the small number of cases that are available for isolated myelosarcoma in children, prognostic statements are difficult. Spontaneous remission of congenital myelosarcoma is reported. However, the majority of cases progressed to AML within months. Comparing with the course of the disease in older patients, one could speculate that the prognosis is rather unfavourable.

We agree, that differential diagnosis between JXG, in particular the Shapiro variant which is seen in this case, and cutaneous manifestations of JMML („myeloid sarcoma“) can be tricky and difficult to differentiate.

In synopsis of all findings, the benign clinical course of Patient 1 (at the age of 10 months the patient was in complete remission and after three years there is still no evidence of disease), the unremarkable laboratory findings (normal blood counts), the imaging (well-defined, homogeneous, hypoechoic lesion without vascularity), the histological (sparing of papillary dermis and periadnexal connective tissue as nicely seen in our case, missing presence and number of (atypical) mitoses and proliferation index with Ki-67) and immunohistochemical findings (positive for macrophage markers CD68 and CD163) our JXG diagnosis seems confirmed and valid.

We ameliorated the photographs to better demonstrate these features.

L 268-292, Ref 37, 38, Fig 2A, B

2. In the case 2, in the histopathological figures, emperipolesis can be seen, as plasma cells or plasmacytoid cells, and some atypical cells. Even not specific for Rosai-Dorfman disease, the association of referred positivity to protein S100 antibody, makes this diagnosis more probable than JXG.

Commentary:

The so-called histiocytoses are rare disorders. More than 100 different subtypes have been described, with a wide range of clinical manifestations, histological and immunohistochemical presentation.
JXG is mostly immunohistochemically negative for S-100 protein and CD1a. However, case reports of S-100 positive JXG were already reported in 1998 (Tomaszewski et al), complemented by a longitudinal observation study in 2009 (Yamamoto et al), which demonstrates, that S-100 protein reactivity cannot be reliably used as definitive marker for differentiating JXG from other histiocytoses such as Rosai-Dorfman disease or indeterminate cell histiocytosis, the latter of which also shows reactivity with additional markers of Langerhans cells, namely CD1a and anti-langerin, absent in our cases. Both these entities frequently show the presence of eosinophils, which in our case were only very subtly present.

Emperipolesis is a condition that can be observed in many physiological and pathological conditions, where hematopoietic cells in living and intact state are seen in the cytoplasm of the host cell without damage. Usually, JXG shows no emperipolesis. Yet, a high degree of emperipolesis in JXG, simulating Rosai-Dorfman disease, has been reported in individual series.

Macrophages in RDD are frequently foamy and can be multinucleated, so that they are difficult to differentiate from JXG. RDD derives from sinus histiocytic macrophages, which are S-100 protein positive, also for fascin, CD68, CD14, CD163 and HLA-DR and negative for CD1a and CD207.

In our case another peculiarity of JXG may be helpful for delineation from RDD, namely iron deposition in siderophages. This phenomenon is well known for the reaction pattern of xanthogranuloma, then entitled xanthosiderohistiocytosis, but has to the best of our knowledge (so far) not been described in RDD.

L 298-319, Ref 39-41 Fig. 6A-D

3. My opinion is that the authors need to review the histopathology and the immunohistochemistry of both cases. If a diagnosis (the same or other) beyond any doubts, is achieved, rewrite the paper, with full discussion about the differential diagnosis.

Commentary:

Patient 1 showed the histological (monomorphic vacuolated cells without cellular atypia or increased or atypical mitosis) and immunohistochemical (negative for S-100 protein, CD1a, CD207 (anti-langerin), toluidine blue histochemistry and c-kit (CD117) and positive for CD68 and CD163), changes typical of JXG.

In Patient 2 the diagnosis was much more difficult and required three biopsies for histological and immunohistochemical work up - including a referral report from Brigham and Women's Hospital - to get the correct diagnosis. The first biopsy, a skin punch showed eosinophils with strong mitotic activity. Immunohistochemistry showed S-100 protein and CD 99 positivity, while CD1a stained negative, typical for a neoplasia of the Ewing / PNET group. The second skin
biopsy from the soft tissue lesion on the infant's left temple was sent to a reference centre (Brigham and Women’s Hospital) and showed sheets of foamy macrophages admixed with mononuclear cells and numerous multinucleated giant cells. There were admixed lymphocytes and neutrophils, and a very prominent stromal haemosiderin deposition. So-called xanthosiderohistiocytosis was regarded as a morphologic variant of xanthoma disseminatum. Just small areas consist of the more monomorphic mononuclear cells similar to those seen in the initial skin biopsy. There was no atypia or pleomorphism and mitoses were scarce. Immunostaining showed strong and diffuse positivity for PU.1 and CD 163, while S-100 protein was negative. It was labelled an unclassified benign xanthogranulomatous lesion, however; the appearances did not fit well with conventional juvenile xanthogranulomatous lesion, so we performed another - computed tomography - assisted - biopsy of the mass in the posterior mediastinum. It showed cellular infiltrates with foamy and prominent nucleoli and eosinophilic granulocytes. Immunohistochemical work-up showed a homogeneous and intensive CD68 and CD163 positivity, while NSE and CD99 showed nonspecific reaction patterns. Langerin and CD 1a, as well as HMB-45 remained negative. S-100 protein showed isolated dendritic background cells; otherwise it remained mostly negative, except for a non-specific reaction in the macrophages. Thus, the definitive diagnosis was xanthogranuloma or a xanthogranulomatous reaction.

We reviewed the histopathology and immunohistochemistry of both cases very conscientiously.

L 223-255 and we ameliorated the photographs 6A-D.

Differential diagnoses are mentioned in detail in the Discussion section.

L 263-319, Ref 37-41

Reviewer 3: Orli Wargon

1. These are interesting cases. The histopathology is the key to the diagnosis. For those who rarely see JXG, the usual benign nature is unclear.

Commentary:

Histiocytoses are rare disorders characterized by the accumulation of cells thought to be derived from dendritic cells or macrophages. Their clinical behaviour ranges from mild to disseminated and sometimes life-threatening forms. Implications for the patient’s health depend on the severity of visceral dysfunction from the histologically benign masses.

Done as suggested: L 71, 72