Case Report

Multiple eruptive milia in chronic graft versus host disease: A case report

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ABSTRACT

Graft-versus-host disease (GVHD) is a significant immunological complication that commonly arises after allogeneic hematopoietic cell transplantation. While cutaneous manifestations of GVHD are well recognized, multiple eruptive milia are an unusual manifestation of cutaneous chronic GVHD. We report a case of periorbital milia developing in a 10-year-old child with chronic GVHD following allogeneic hematopoietic stem cell transplantation. This case illustrates an uncommon cutaneous manifestation of chronic GVHD, in which immune-mediated epidermal disruption may contribute to secondary milia formation.

Key words: Graft versus host disease, Graft-versus-host disease, Milia

Graft-versus-host disease (GVHD) is a significant immunological complication that arises after allogeneic hematopoietic cell transplantation (HCT) or, less commonly, after solid organ transplantation or non-irradiated blood. GVHD occurs when immunocompetent donor T cells identify recipient antigens as foreign, resulting in the activation and proliferation of donor T cells that target host tissues, leading to tissue damage and inflammation [1]. Acute GVHD manifests within the initial 100 days following allogeneic HCT. It mainly affects the skin, the gastrointestinal tract, and the liver [2]. Chronic GVHD often manifests after day 100. It may arise *de novo*, as a progression from acute GVHD, or as an overlap syndrome with features of both acute and chronic manifestations [1,2]. Up to 90% of individuals with GVHD have skin involvement, which is the most common organ affected. Cutaneous presentation is typically the initial symptom. In contrast to chronic GVHD, where sclerotic or lichen-planus-like lesions are more common, acute forms occur in nearly one-third of HCT patients and are typically characterized as folliculocentric maculopapular to morbilliform eruptions [3]. However, cutaneous manifestations can vary, and a number of distinct phenotypes have been identified, including ichthyosis-like, dyspigmentation-like, psoriasiform, erythema multiforme-like, dermatomyositis-like, lupus-erythematosus-like, keratosis pilaris-like, and pityriasis rosea-like forms [3]. Milia are small, benign, superficial keratin-containing cysts that manifest as multiple dome-shaped white papules.

We report a case of a 10-year-old child who developed chronic GVHD following a bone marrow transplantation for β-thalassemia in the form of multiple eruptive milia, an atypical manifestation of chronic GVHD. To our knowledge, no similar cases have been reported in the existing literature.

CASE REPORT

A 10-year-old female child presented with a complaint of periocular skin lesions for a duration of 6 months. She was a known case of β-thalassemia major and had undergone allogeneic hematopoietic stem cell transplantation from a matched donor at the age of 4 years. Subsequently, she developed chronic GVHD involving the liver, oral mucosa, and eyes. Three months following transplantation, while receiving systemic immunosuppressive therapy (tacrolimus, mycophenolate mofetil, and prednisolone), the patient developed multiple asymptomatic whitish papules over the periocular region and upper face. There was no history of similar prior lesions, local trauma, topical medication use, or relevant family history.

On external examination, multiple approximately 1 mm, firm, dome-shaped, white papules were clustered over the upper and lower eyelids and adjacent upper facial skin, without surrounding erythema, ulceration, or

Access this article online

Received - 02 April 2026
Initial Review - 21 April 2026
Accepted - 21 May 2026

DOI: 10.32677/ijcr.v12i6.8212

Quick Response code

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discharge (Fig. 1). Ophthalmologic examination revealed features of ocular surface disease, including conjunctival injection and punctate superficial keratitis, consistent with ocular GVHD, for which the patient was maintained on regular topical lubricants.

A biopsy was performed, where histopathological results revealed the presence of follicular cysts and comedones (Fig. 2).

Based on the biopsy result and the history of abrupt onset following stem cell transplant, a diagnosis of secondary milia associated with GVHD was established. Given the benign, asymptomatic nature, clinical observation was recommended. The patient has been followed up for several months, during which the lesions have remained clinically stable, with no increase in size or number and no reported symptoms or complications.

DISCUSSION

Milia are described as small (<3 mm), white, benign superficial keratinous cysts. Furthermore, they can be subdivided into primary, secondary, or genodermatoses-associated milia. Primary milia are thought to originate from the sebaceous collar of vellus hairs (lower infundibulum), while secondary milia often arise from the eccrine sweat ducts [4]. An updated classification system for milia has been proposed in the literature. Primary milia can be classified as congenital, benign primary milia of children and adults, milia en plaque, nodular grouped milia, multiple eruptive milia, nevus depigmentosus with milia, and genodermatosis-associated milia [5].

From a pathophysiological perspective, milia represent a disorder of keratin retention and abnormal follicular epithelial differentiation, resulting in keratinous cysts within the superficial dermis. Histologically, they appear as small epidermoid cysts lined by stratified squamous epithelium and containing lamellated keratin [6]. Dermoscopy may support the diagnosis, typically showing well-defined, round, white-to-yellowish homogeneous lesions that help differentiate milia from syringomas, xanthelasma, or sebaceous hyperplasia.

Figure 1: External photograph showing multiple milia over the right periocular area

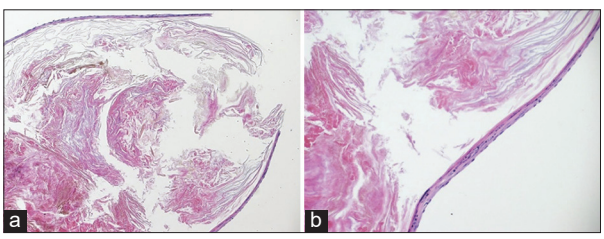

Figure 2: Hematoxylin and eosin-stained sections (a) ×100, and (b) ×200 showing a cyst filled with keratin and squamous epithelial lining

Multiple eruptive milia define the sudden appearance of multiple milia in large numbers. Where it can arise spontaneously, multiple eruptive milia have also been described as a familial disorder. Second, milia could develop in areas of prior skin trauma, such as dermabrasion, burns, skin peeling, and radiotherapy. Diseases such as epidermolysis bullosa, lichen planus, and contact dermatitis can trigger secondary milia formation. In addition, medications reported to induce secondary milia include topical steroids, 5-fluorouracil, and penicillamine, and more recently, with targeted therapies such as tyrosine kinase inhibitors [7,8].

Milia are not typically associated with immune deficiency as a primary etiologic factor. However, it has been reported that milia en plaque can occur in immunosuppressed patients, such as organ transplant recipients, where it was believed to be related to immunosuppressive therapy [9,10]. These reports involve solid-organ transplantation, particularly renal transplant, where milia en plaque has been associated with cyclosporine therapy without concomitant GVHD. In contrast to previous studies, the association with GVHD, as observed in our case, suggests that immune-mediated epidermal injury and subsequent re-epithelialization may contribute to the development of eruptive milia. This mechanism aligns with observations in other traumatic or blistering conditions, where disruption of the dermoepidermal junction predisposes to milia formation [11].

Clinically, milia are asymptomatic but may cause cosmetic concern, particularly when extensive. Congenital milia typically resolve spontaneously and do not require intervention. However, the other forms of primary milia, as well as secondary milia, may persist. Management is primarily conservative and guided by patient preference, with treatment indicated for cosmetic or symptomatic reasons. First-line options include simple mechanical extraction through a sterile needle incision, followed by expression using a comedone extractor or curette. Adjunctive therapies include topical retinoids, which promote epidermal turnover and reduce the risk of recurrence, as well as procedural interventions such as electrocautery or electrodesiccation [4].

CONCLUSION

This case highlights a previously unreported association between multiple eruptive milia and GVHD, suggesting that immune-mediated epidermal injury may contribute to

their pathogenesis. This observation broadens the clinical spectrum of GVHD-related cutaneous manifestations and underscores the importance of considering systemic and immunological factors in such presentations.

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Funding: Nil; Conflicts of interest: Nil.

How to cite this article: Al-Amoudi LO, Al-Shehri AS, Al-Zaid TJ, Al-Faky YH. Multiple eruptive milia in chronic graft versus host disease: A case report. Indian J Case Reports. 2026;12(6):377-379.