DOI: https://doi.org/10.3126/njdvl.v20i2.47326

Chronic Bullous Disease of Childhood: A Case Report and Review of Literature of Bullous Diseases in Children

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Abstract

We describe a case of a 5-year-old boy who presented with multiple mild itchy and painful blisters predominantly over his trunk and limbs for one year with multiple tense bullae with hypopyon signs resulting in a half-and-half appearance of the blisters. A skin biopsy showed subepidermal separation with predominantly neutrophils and eosinophils in the bulla cavity and mixed infiltrate in the papillary dermis. We would like to report a case of chronic bullous disease of childhood and review its differentials for diagnostic approaches to blistering disease in children..

Key words: Bullous disease; Children;Histopathology; Immunohistochemistry

Introduction

Bullous disease in children, is a complicated heterogenous and challenging group of disorders to dermatologists. Pemphigus vulgaris and pemphigoid with an incidence of 0.20 and 0.12 per 100,000 population, respectively were commonest bullous disease.[1] Dermatological disease constitutes 30% of outpatient visits to pediatricians, and 30% of visits to dermatologists comprises children.[2] Clinically, blister formation is the most common hallmark of bullous disease, requiring routine histopathological and immunofluorescence examination based on the location and morphology of blisters. It is classified as inherited, autoimmune, infective, and miscellaneous disorders.[3] Inherited disorders comprise epidermolysis bullosa (EB), porphyria cutanea tarda, congenital erythroderma, and incontinentiapigmenti. Autoimmune disorders include linear IgA dermatosis or chronic bullous disease of childhood (CBDC), dermatitis herpetiformis (DH), pemphigus, pemphigoid, epidermolysis bullosa aquisita (EBA), and bullous systemic lupus erythematosus. Infectious disease includes bullous impetigo, Staphylococcal Scalded Skin Syndrome (SSSS), herpes, candidiasis, congenital syphilis, and scabies. Miscellaneous group comprises Steven-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), transient acantholytic dermatosis, eczema, insect bites, trauma, acute contact dermatitis, erythema multiforme, and miliaria crystalline. Most of these disorders in children are rare and misdiagnosed.[4] Here we report a 5-year-old male child with CBDC, emphasizing other differential diagnoses to assess the diagnostic criteria for bullous disease in children.

Case report

A 5-year-old boy presented with multiple mild itchy and painful blisters predominantly over his trunk and limbs for one year. Blisters presented for 5-8 days, ruptured spontaneously and healed with post-inflammatory hyperpigmentation in 2-4 weeks. There were multiple episodes of recurrence and remission.

Funding: None
Conflict of Interest: None

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Date of Submission: July 9th 2022
Date of Acceptance: September 10th 2022
Date of Publication: October 1st 2022

How to cite this article
Pradhan S, Jha K, Kumari P, Shrestha S, Jha AK.Chronic Bullous Disease of Childhood: A Case Report and review of literature of bullous diseases in children. NJDVL 2022;20(2):69-75 https://doi.org/10.3126/njdvl.v20i2.47326

The child had been on a tapering oral prednisolone for two and a half months at the local center, without much improvement. The child was afebrile, had achieved normal milestones, and was fully vaccinated. Family history was not significant. Dermatological examination revealed numerous tense vesicles and bullae in the erythematous base. There were multiple annular erythematous crusted plaques varying in size, surrounded by pus-filled bullae and vesicles on the trunk, gluteal region, upper and lower extremities, sparing the face and perioral area (Figure 1a, 1b,and 1c). Some bullae were filled with clear fluid, whereas others contained clear and yellow fluid in the upper and lower half, forming a hypopyon. Multiple tense bullae with hypopyon signs resulted in half-and-half appearance of the blisters (Figure 2a).

Moreover, vesicles and bullae were arranged in an annular pattern around the edge of an erythematous plaque giving the "cluster of jewels" appearance (Figure 2b). On mucosal examination, oral, ocular, and genital mucosa was normal. Nikolsky's sign was negative. Based on history and examination, differential diagnosis of chronic bullous disease of childhood (CBDC), bullous pemphigoid, IgA pemphigus, bullous impetigo, dermatitis herpetiformis, epidermolysis bullosa acquisita, and subcorneal pustular dermatosis was made. Routine blood investigations showed an increase in total White Blood Cell (WBC)count of 25,510/cumm and serum albumin of 3.3 gm/dl where rest examinations were within normal limit. Pus culture from the bulla was negative. Histopathological examination of the skin biopsy demonstrated subepidermal separation with predominantly neutrophils and eosinophils in the bulla cavity and mixed infiltrate in the papillary dermis (Figure 3a and 3b). However, direct immunofluorescence (DIF) was negative. The clinical diagnosis of chronic bullous disease of childhood was confirmed.

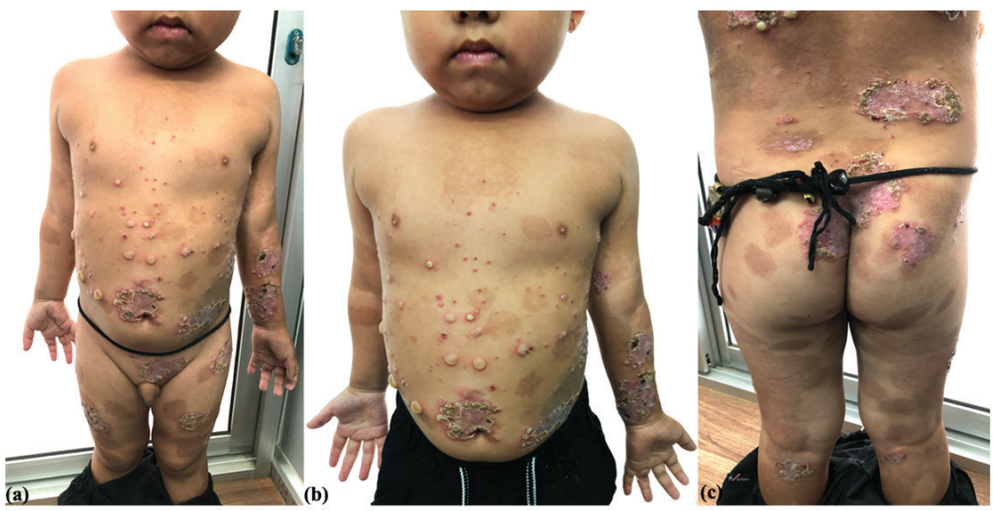

Figure 1: Multiple tense vesicles and bullae with erosions and crusts over the trunk (a), extremities (b), and back (c).

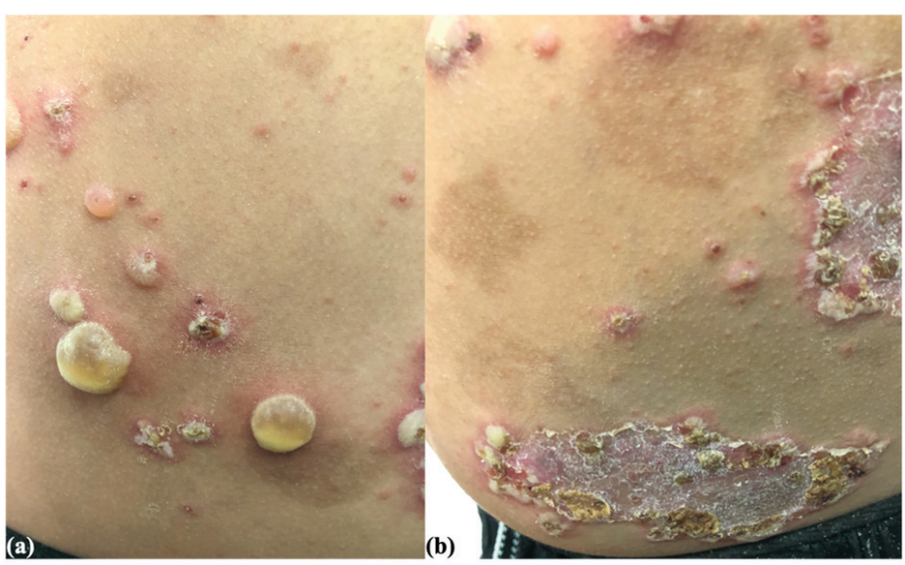

Figure 2: Half-and-half aspects of pustule – "hypopyon sign" over the left lower abdomen (a); and vesicles and bullae arranged in an annular pattern around the edge of an erythematous plaque giving the "cluster of jewels" appearance over the right lower abdomen (b).

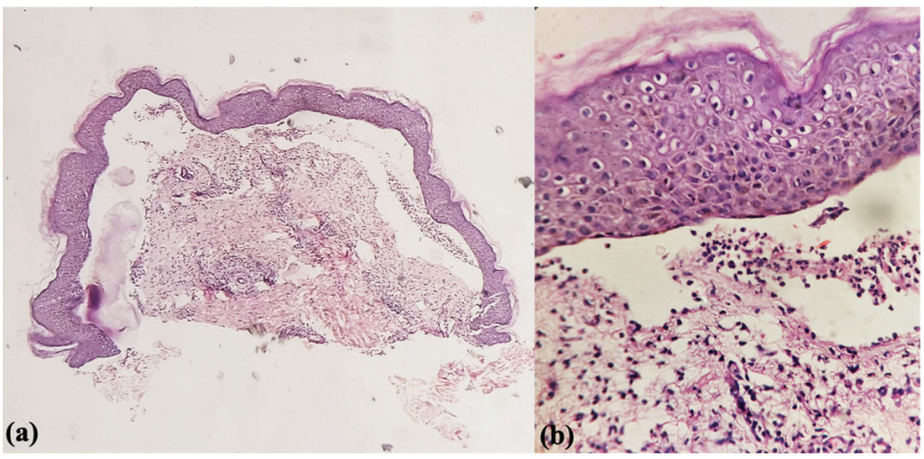

Figure 3: Histopathological view of the skin biopsy specimen (a) Section showing sub-epidermal separation (Hematoxylin-eosin [HE], original magnification ×40) and (b) Section showing inflammatory infiltrate in the bullous cavity and papillary dermis (Hematoxylin-eosin [HE], original magnification ×100).

Discussion

Bullous diseases are uncommon in children and tend to affect the quality of life. Bullous disease can be challenging due to its frequent overlapping of clinical and histopathological features, requiring an appropriate diagnostic approach. In this case, the diagnosis of CBDC was based on the unique feature of the hypopyon formation in the form of blisters half-filled with clear fluid and half with pus along with cluster of jewels appearance diagnosed clinically and histopathologically. Hypopyon formation is classically described in subcorneal pustular dermatosis, a rare entity characterized by the presence of sterile pustules and predominant flexural involvement. It is also observed in bullous impetigo and staphylococcal scalded skin syndrome. However, we discuss the clinical presentation of common bullous diseases in children, emphasizing on prevention of misdiagnosis (Table1).

Chronic bullous disease of childhood or Linear Immunoglobulin A bullous dermatosis

Chronic bullous disease of childhood (CBDC) is the most common acquired autoimmune blistering disorder occurring without sexual predilection. It usually occurs at 6 months to 10 years, with a mean age of 4.5 years.[5] It is presented with abrupt onset of tense, clear, or hemorrhagic vesicles and bullae on normal or erythematous skin. The cluster of jewels forming annular or arciform bullae usually arise around revolving lesions surrounding the central crust. The clinical clue of jewel-like cluster coalescing vesicles consistent with our findings has only been mentioned in 4 cases.[5] The eruption occurs on the face, trunk, and extremities.[6] Mucocutaneous involvement is common in neonates, whereas cutaneous lesions are common in children.[7] CBDC is mainly diagnosed by hematoxylin-eosin-stained biopsy and immunofluorescence testing. Histopathology is characterized by a subepidermal blister with neutrophilic infiltration in the papillary dermis with mononuclear cells and eosinophils.[6]Immunofluorescence testing of perilesional skin shows linear IgA deposition along the basement membrane zone. The common initial differentials are bullous impetigo and epidermolysis bullous acquisita. CBDC is often idiopathic and may be triggered by infections, drugs, vaccinations, ultraviolet radiation, or malignancy.[8] CBDC have a good prognosis.[6]

Dermatitis Herpetiformis

Dermatitis herpetiformis (DH) is the most common chronic autoimmune disease of celiac disease in childhood.[9] It has equal gender prevalence with ages ranging from 2 to 7 yearsto a mean of 14 years.[10,11] DH in childhood is presented with intensely pruritic vesicles, erythematous papules, and urticarial plaques with small excoriations and crusts.[12] It mainly affects the extensor surface of the limbs, buttocks, shoulders, nape of neck, and scalp sparing mucous membrane involvement.[12]The involvement of presentations with chronic urticaria[13] and digital petechiae[14] has also been described in children. It has been reported that gluten-sensitive enteropathy is present in almost all children with DH. However, only a small fraction of them (10%) has a diagnosis of celiac disease with DH.[15] Histopathology examination shows characteristics of the subepidermal blister with neutrophilic with occasional eosinophilic microabscesses within the dermal papillae and fibrin deposition.[12] On DIF examination of perilesional skin show the presence of granular deposition of IgA within the dermal papillae, accompanied by C3.[12] The clinical features were not consistent with our case. The prognosis of DH in childhood remains unclear due to the possibility of long remissions and relapses due to poor adherence to the gluten-free diet.[12]

Epidermolysis Bullosa Acquisita

Epidermolysis bullosa acquista (EBA) is a rare chronic immunobullous subepidermal disease in childhood with no gender or racial predilection reported. It can be presented anytime during childhood, initiating at infancy.[12] EBA comprises two main types comprising of non-inflammatory mechanobullous and inflammatory type. Non-inflammatory type is more common in adults presenting with acral blisters at trauma sites, frequent scarring, milia pigmentary changes, and nail dystrophy. Inflammatory type is common in children aged <5 years, mimicking BP or other inflammatory bullous disorders presenting with pruritic, tense bullae, hemorrhagic lesions with pigmentary changes.[16] Mucosal involvement of the oral cavity is more common in childhood EBA.[16] Type VII collagen is part of the anchoring fibrils of the epidermal basement membrane as the target autoantibodies where noncollagenous (NC)1 domain of type VII collagen frequently targets adult patients, where reactivity to the NC2 domain and triple helical domain targeted in childhood EBA.16 Histopathologic examination of the lesions reveals sub-epidermal bullae with neutrophilic inflammatory infiltrate mixed with eosinophils may differ as its types. DIF demonstrates linear immunoglobulin deposition (commonly IgG) along the BMZ, with a u-serrated pattern similar in adults and children. Salt-split skin demonstrates dermal staining. EBA in the pediatric population has been reported to occur between 2 weeks and 17 years.[16] EBA in adults has been associated with Crohn's disease, whereas in childhood EBA includes Immunodysregulationpolyendocrinopathology enteropathy X-linked (IPEX) syndrome, celiac disease, pemphigus vulgaris, and malignant lymphoma, penicillamine, squaric acid dibutyl ester immunotherapy for alopecia areata, and various autoantibodies.[16] The clinical features of EBA differed from our case of CBDC. The prognosis of EBA in children is better than in adults, with remission within 1 to 4 years.[12]

Mucous Membrane (cicatricial) Pemphigoid

Mucous membrane (cicatricial) pemphigoid (MMP) is a group of immunobullous subepidermal conditions rare in childhood.[12] It is commonly presented with generalized eruption involving the face, trunk, and limbs characterized by annular, polycyclic, or target-like lesions. It predominantly involves mucous membranes leading to various degrees of scarring.[12] In a review of 18 cases, the average age of onset was 10.3 years (range from 20 months to 18 years).17 BP180, laminin 5, type VII collagen, beta 4 subunit of $\alpha 6\beta 4$ integrins, multiple target antigens for its clinical heterogenicity have been described.[12] Histopathology of MMP is similar to BP with subepidermal blisters comprising perivascular lymphohistiocytic infiltration, plasma cells, neutrophils, and fewer eosinophils. DIF may reveal IgA and/or IgG and/or C3 deposition in a linear pattern at the dermal-epidermal junction.[12] However, in cases of anti-laminin 332 MMP, salt-split results in dermal staining. Indirect immunofluorescence detects circulating antibodies against epithelial basement membrane constituents in about 50% of cases.[12] The histopathology and clinical manifestation of MMP was not seen in CBDC. The favorable prognosis of MMP in children depends upon clinical manifestation, with few cases extending into adulthood.[12]

Bullous Pemphigoid

Bullous pemphigoid (BP) is a subepidermal immunobullous disorder rarely observed in children characterized by autoantibodies to BP antigens 180 and 230.[16] In a study of 78 cases, two peaks of onset in childhood, with 53% of cases occurring in the first year of life at a median age of 4 months and the second peak at a median age of 8 years in 47% of cases were found.[18] BP presents with tense bullae, sometimes hemorrhagic from normal or inflamed skin with urticarial plaques in annular or polycyclic patterns commonly occurring on the groin, axilla, abdomen, and inner thigh.[12] Acral (palmar and plantar) involvement is common in infantile BP.[16] Childhood BP has a higher frequency of vulvar involvement.16 Facial involvement in BP can easily lead to misdiagnosis of impetigo.[12] Histopathology is characterized by subepidermal blistering with an intact overlying epidermis with no necrosis infiltrated with eosinophils, neutrophils, and lymphocytes.[12]DIF reveals a linear deposition of IgG and C3 with less frequent IgM and IgA.[19]The clinical and histopathological features of our case distinguished from BP. The prognosis of children with BP is good, with cases lasting 1 year or less.[12]

Bullous impetigo (Staphylococcal impetigo)

Bullous impetigo (BI) is a highly contagious infection mainly affecting neonates and children where *S. aureus* is isolated from the skin lesions.[20] It is presented with large, superficial, fragile bullae with ulceration. Only remnants of bullae are observed with annular or oval superficial erosions with a typical collarette of scale at the periphery of the bullae.[20]Blister is formed due to the splitting of the granular cell layer by exfoliative toxins A and B.[21] Histopathology of intact pustule reveals typical subcorneal accumulation of neutrophils in clusters or chains of Gram-positive cocci after staining.[21] The clinical and histopathological features of our case were inconsistent with BI.

Staphylococcal scalded skin syndrome

Staphylococcal scalded skin syndrome (SSSS) is a rare disorder with clinical features varying from superficial localized blisters to generalized exfoliation.[22]SSSS commonly affects neonates of 3-15 days of age and

children less than 5 years of life due to an undeveloped immune system to produce antibodies against the ETs and their inadequate renal capacity to excrete the pathogenic toxins.[22] The clinical features of SSSS comprise fever with erythematous patches over the body with the development of large superficial fragile blisters appearing reddish or scalded on the chest, axilla, and gluteal region, sparing the mucosa.[22] Nikolsky's sign is usually positive. The diagnosis is usually based on the culture reports for the growth of *Staphylococcal aureus*. Histopathology is characterized by intraepidermal cleavage without necrosis. The clinical features, nikolsky's sign and histopathology of our case were inconsistent with SSSS. The prognosis of SSSS is good.

Subcorneal pustular dermatosis

Subcorneal pustular dermatosis (SCPD, Sneddon-Wilkinson disease) is a rare chronic, relapsing, pustular eruption in childhood. Only 15 pediatric SCPD have been reported in the literature, including palmar and plantar pustules.[23] It may be associated with malignant neoplasms such as multiple myeloma, chronic lymphocytic leukemia, and thymoma. SCPD mainly involves the trunk, intertriginous areas, flexor aspects of the limbs sparing the face, and mucous membrane.[23] The clinical hallmark sign is the lower half of the lesion presented with a sterile purulent content, and the upper half is a serous one described as a "half-and-half" sign. Histopathology of SCPD lesion indicates subcorneal pustules and dermal infiltrate containing mainly neutrophils with few eosinophils, little or no spongiosis without acantholysis. DIF is negative. Although SCPD is rare in childhood, it must be considered a possible cause of sterile pustular eruptions. Even though similar findings of half-and-half sign persisted, histopathological examination along with cluster of jewel appearance assisted in confirming our diagnosis as CBDC. Physical examination, complete blood count, and serum biochemistry investigations are recommended to exclude any pathology association.[23]

Conclusion

Bullous disorders in children are a large group of disorders with frequent overlapping of clinical, histopathological, and immunological features, which require proper comprehensive diagnostics approaches for proper treatment. Moreover, in this case, the typical presentation of half-and-half signs and cluster of jewel appearance along with histopathology helped us confirm our diagnosis as CBDC from other differentials. Special appropriate considerations should be made in diagnosing bullous diseases in children to avoid misdiagnosis.

Table1: Bullous disease in children

	Cutaneous lesions	Most common distribution	Pruritus	Mucosal involvement	Histopathology	Direct Immunofluorescence
CBDC	-Tense vesicles on normal/urticarial patches - "Cluster of jewels"	-Face, extremities, genital area, and trunk	±	Common	-Subepidermal blisters -Inflammatory infiltrate with Eos and PMN	-Linear IgA along dermal epidermal junction
DH	-Polymorphic (small vesicles, erythematous papules and urticarial plaques) -erosions -Crusts	-Extensor surface of the limbs -Buttocks -Shoulders -Nape of neck -Scalp	++++	None	-Subepidermal blisters with neutrophils micro abscesses within dermal papillae -Fibrin deposition	-Granular deposits of IgA within dermal papillae
EBA	-Mechanobullous type: blisters, erosions, crusts, and scars in exposed sites -Inflammatory type: Tense bullae (similar to CBDC or BP)	-Mechanobullous type: At sites of trauma over acral bony prominences -Inflammatory type: Normal, erythematous or urticarial skin (similar to CBDC or BP)	Mechanobullous type: _ Inflammatory type: ±	Frequent and severe (oral mucosa)	-Subepidermal blisters -Inflammatory infiltration with neutrophils and Eos	-Linear IgGdeposition at basement membrane zone
MMP	-Only or predominantly mucous membranes affected with blisters and erosions, scarring of conjunctiva	-Head, Face, trunk, and limbs	++++	Frequent (oral mucosa and conjunctiva)	-Subepidermal blisters -Perivascular lymphohistiocytic infiltration with plasma cells, neutrophils, and fewer Eos	-Linear deposits of IgA and/or IgG and/or C3 at dermal epidermal junction.

BP	-Large, tense blisters that may be hemorrhagic	-Acral (palms and soles) -Flexural areas (inner thighs, forearms, axillae, lower abdomen, and groin)	± to ++++	Frequent	-Subepidermal blisters with Eos	-Linear deposits of IgG or C3 at basement membrane zone
BI	-Large, superficial, fragile bullae with ulceration	-Anogenital area -Buttocks	_	None	-Subcorneal accumulation of neutrophils in clusters	Negative
SSSS	-Large, superficial fragile blisters	-Chest -Axilla -Gluteal region	_	None	-Acantholytic cells with subcorneal blister	Negative
SCPD	-lower half presented with a sterile purulent content and the upper half a serous one described as "half-and-half" sign.	- Trunk -Intertriginous areas -Flexor aspects of the limbs	_	None	-Subcorneal pustules -Dermal infiltrate containing neutrophils and few Eos	Negative

CBDC, Chronic bullous disease of childhood; DH, Dermatitis Herpetiformis; EBA, Epidermolysis Bullosa Acquisita; MMP,Mucous Membrane (cicatricial) Pemphigoid; BP, Bullous Pemphigoid; BI, Bullous impetigo; SSSS, Staphylococcal scalded skin syndrome; SCPD, Subcorneal pustular dermatosis;PMN, Polymorphonuclear Neutrophils; Eos, Eosinophil

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