

1 **Childhood Erythrodermic Lichen Planus Pemphigoides after Nonavalent Human**  
2 **Papillomavirus Vaccination**

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## 28 INTRODUCTION

29 Lichen Planus Pemphigoides (LPP) is an uncommon autoimmune blistering disease characterized by  
30 clinical and microscopic findings of lichen planus (LP), and a subepidermal blistering disease with  
31 antibodies to the basement membrane, similar to bullous pemphigoid (BP). The disease is rare in  
32 adults and rarer in pediatric age with only 17 cases described so far (1-7,13). LPP is usually  
33 idiopathic, although it has been related to some drugs in adults. As for children, LPP has been related  
34 to varicella infections (2, 3) and triggered by henna tattoo (5) or excessive aromatic retinoid (7). To  
35 our knowledge, this is the first case of pediatric erythrodermic LPP described after nonavalent  
36 Human Papillomavirus (HPV) vaccination.

## 37 CASE REPORT

38 An 11-year-old boy presented with an extremely pruritic, diffuse rash for 7 weeks. The eruption has  
39 started 2 weeks after receiving the first dose of Human Papillomavirus Vaccine (Gardasil 9®) with  
40 isolated papules that flowed into a widespread dermatitis. He had a history of atopic dermatitis, was  
41 up to date on all vaccines and was taking no medication. Physical examination found a patient with  
42 dry erythroderma involving more than 90% of the body surface according to Wallace's rule of nine.  
43 with the presence of purplish papules on the face, neck, trunk, upper and lower extremities  
44 including palms and soles, as well as tense, hemorrhagic blisters on the legs and feet. Vesiculo-  
45 bullous lesions were present both on the papular lesions and on normal skin, appearing 5 weeks  
46 after the development of papules. (fig. 1, 2). Mucous membranes and nails were spared. Nikolsky's  
47 sign was negative. Histological examination of a lichenoid lesion from the thigh showed  
48 hyperkeratosis with parakeratosis, focal hypergranulosis, acanthosis, with some apoptotic  
49 keratinocytes, interface dermatitis with a dense lichenoid infiltrate of lymphocytes and rare  
50 eosinophils (fig. 3), whereas histopathology of a bullous lesion on the leg revealed a subepidermal  
51 blister containing eosinophils and neutrophils in the blister fluid and a mixed inflammatory infiltrate  
52 in the dermis (fig. 4). Direct immunofluorescence showed linear C3 deposits along the basement

53 membrane. (supplementary fig.). ELISA from serum was positive for PB180 antibody (120 U/ml,  
54 (normal <9 U/ml) and slightly positive for PB230 antibody (10,50 U/ml, normal<9 U/ml).A  
55 diagnosis of LPP was made. The patient was treated with oral deflazacort 1,5 mg/kg/day,  
56 antihistamines and topical steroids with rapid improvement and clearing of the itching eruption. At  
57 6-week follow-up, the patient had only residual post inflammatory hyperpigmentation. The patient's  
58 parents were advised to avoid further HPV vaccine injections to their son.

## 59 DISCUSSION

60 LPP is a rare, autoimmune, sub-epidermal bullous disease characterized by the co-existence of both  
61 LP and BP, although the relationship between these two disorders is more complex. Clinical  
62 findings include two primary skin lesions, i.e. lichenoid papules and plaques and tense,  
63 subepidermal blisters located both on the lichenoid plaques and on the uninvolved skin (8, 9),  
64 differently from bullous lichen planus, in which bullae are limited to longstanding lichen planus  
65 lesions. The onset of lichenoid lesions usually precedes the onset of bullae . Mucosal and nail  
66 involvement may occur but is uncommon. Palmoplantar involvement is seen more often in children.  
67 The erythrodermic form is rare, being reported in just 11 cases in adults but only in one case in  
68 pediatric age. Thus, our patient seems to represent the second case of erythrodermic pediatric LPP  
69 (6). The pathogenesis of LPP can be explained by the phenomenon of "epitope spreading". It has  
70 been hypothesized that a lichenoid inflammatory attack to the basal cell layers and basal membrane  
71 can expose antigens and promote the development of an autoimmune response, targeting proteins of  
72 the epidermal basement membrane including type XVII collagen (COL17) also known as PB180  
73 antigen (11, 12).

74 Although usually idiopathic, LPP has been related to drugs such as cinnarizine, captopril, ramipril,  
75 simvastatin, antituberculous medications, phototherapy, gliptins, nivolumab, enalapril and rarely to  
76 malignancies. LPP has also been reported to be triggered by viral infections such as varicella (2, 3),  
77 Hepatitis B virus (13, 14) and lastly, pharyngitis in the only pediatric case of erythrodermic LPP (6).

78 Gardasil 9 ® is the nonavalent HPV vaccine (9vHPV) licensed in 2014 that contains an additional  
79 five cancer-causing HPV types (HPV31, 33, 45, 52, and 58) in addition to the four more common  
80 HPV types (16, 18, 6 and 11) (15). It has twice the concentration (500 mg) of aluminum  
81 hydroxyphosphate as an adjuvant (16) compared to 4-valent HPV vaccine.

82 Adverse events to HPV vaccination have been previously reported, including local reactions at the  
83 injection site such as granulomas, lipoatrophy; cellulitis, sub-cutaneous emphysema, mainly related  
84 to the aluminum vaccine content, as well as erythema multiforme, dermatographism, urticaria,  
85 erythema nodosum, linear IgA bullous dermatosis (17-19). Very recently, a lichenoid eruption  
86 following HPV vaccine has also been described (20). To the best of our knowledge this is the first  
87 case of LPP, in its erythrodermic variant, following nonavalent HPV vaccination (Gardasil 9®). In  
88 our patient, for ethical reason, we could not perform a re-challenge but, the pattern of lichenoid  
89 reaction followed by the appearance of the bullae, the temporal relationship between the development  
90 of LPP and the vaccination, and the complete healing of the eruption, suggest that the HPV vaccine  
91 was the probable triggering event.

92

#### 93 ABBREVIATION AND ACRONYM LIST

94 LPP: Lichen Planus Pemphigoides

95 LP: Lichen Planus

96 HPV: Human Papillomavirus

97 COL17: Type XVII collagen

98 ELISA: Enzyme-Linked immunosorbent assay

99 BP: Bullous Pemphigoid

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## 102 REFERENCES

- 103 1. Cohen DM, Ben-Amitai D, Feinmesser M, **et al.** Childhood Lichen Planus Pemphigoides: A  
104 Case Report and Review of the Literature. *Pediatric Dermatology* 2009.26:569-574.
- 105 2. Mohanarao TS, Kumar GA, Chennamsetty K, **et al.** Childhood lichen planus pemphigoides  
106 triggered by chickenpox. *Indian Dermatol Online J* 2014. 5(Suppl 2): S98-S100.
- 107 3. Ilknur T, Akarsu S, Uzun S, **et al.** Heterogeneous disease: a child case of lichen planus  
108 pemphigoides triggered by varicella. *J Dermatol* 2011. 38:707-10.
- 109 4. Duong B, Marks S, Sami N, **et al.** Lichen planus pemphigoides in a 2-year-old girl: Response  
110 to treatment with methotrexate. *J Am Acad Dermatol* 2012. 67, 4, e-154–e156.
- 111 5. **Goldscheider I, Herzinger T, Varga R, et al.** Childhood Lichen Planus Pemphigoides: Report of Two  
112 Cases Treated Successfully with Systemic Glucocorticoids and Dapsone. *Pediatric Dermatology* 2014.  
113 31:751-3.
- 114 6. Maouni S, Ouïam EA, Asmae S, **et al.** A Pediatric Case of Erythrodermic Lichen Planus  
115 Pemphigoides. *J Clin Trials* 2019. 8: 359.
- 116 7. Pierini AM, Bussy RF, Souteryand P **et al.** Liquen Plano Ampollar: Estudio de dos casos  
117 infantiles y revision de la inmunopatologia [Bullous lichen planus. Study of two cases in  
118 children and review of immunopathology]. *Arch Argent Dermatol* 1981. 31:217-228.
- 119 8. Hubner F, Langan EA, Recke A. Lichen Planus Pemphigoides: From Lichenoid Inflammation  
120 to Autoantibody-Mediated Blistering. *Front Immunol* 2019. 10:1389.
- 121 9. **Archer CB, Cronin E, Smith NP.** Diagnosis of Lichen Planus Pemphigoides in the absence of  
122 bullae on normal-appearing skin. *Clin Exp Dermatol* 1992. 17:433-6.
- 123 10. **Zaraa I, Mahfoudh A, Sellami MK et al.** Lichen planus pemphigoides: four new cases and a  
124 review of the literature. *Int J Dermatol* 2013. 52: 406-412.
- 125 11. **Matos-Pires E, Campos S, Lencastre A,** **et al.** Lichen Planus Pemphigoides. *J Ger Soc*  
126 *Dermatol* 2018. 16:335-7.

- 127 12. Chan LS, Vanderlugt CJ, Hashimoto T, et al. Epitope spreading: Lessons from autoimmune  
128 skin disease. *J Invest Dermatol* 1998. 8:331-6.
- 129 13. Jang SH, Yun SJ, Lee SC, et al. Lichen planus pemphigoides associated with chronic hepatitis  
130 B virus infection. *Clin Exp Dermatol* 2015. 40:868-71.
- 131 14. Flageul B, Hassan F, Pinguier L, et al. Lichen pemphigoid associated with developing  
132 hepatitis B in a child. *Ann Dermatol Venereol* 1999. 126(8-9):604-7.
- 133 15. Toh ZQ, Kosasih J, Russell FM, et al. Recombinant human papillomavirus nonavalent  
134 vaccine in the prevention of cancers caused by human papillomavirus. *Infect Drug Resist*  
135 2019. 12: 1951–1967
- 136 16. Cervantes JL, Doan AH. Discrepancies in the evaluation of the safety of the human  
137 papillomavirus vaccine. *Mem Inst Oswaldo Cruz*. 2018. 113: e180063.
- 138 17. Longueville C, Doffoel-Hantz V, Hantz S, et al. Gardasil®-induced erythema nodosum. *Rev*  
139 *Med Interne* 2012. 33:17-18
- 140 18. Ikeya S, Uirano S, Tokura Y. Linear IgA bullous dermatosis following human papillomavirus  
141 vaccination. *Eur J Dermatol* 2012. 22:787-788.
- 142 19. Katoulis AC, Liakou A, Bozi E, et al. Erythema multiforme following vaccination for human  
143 papillomavirus. *Dermatology*. 2010. 220:60-2.
- 144 20. Laschinger ME, Schleichert RA, Green B. Lichenoid drug eruption after human  
145 papillomavirus vaccination. *Pediatr Dermatol* 2015;32:e48. \_

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## 148 LEGEND OF FIGURES

149 Figure 1: Lichen Planus Pemphigoides: dry erythroderma, with the presence of purplish papules on  
150 the trunk, upper and lower extremities including palms and soles

151 Figure 2: Lichen Planus Pemphigoides: dry, erythematous patches with vesiculo-bullous elements,  
152 some with hemorrhagic content

153 Figure 3: Lichen Planus Pemphigoides: histopathology of a papule showed hyperkeratosis with  
154 parakeratosis, focal hypergranulosis, acanthosis, with some apoptotic keratinocytes, interface  
155 dermatitis with a dense lichenoid infiltrate of lymphocytes and rare eosinophils (H&E 25X)

156 Figure 4: Lichen Planus Pemphigoides: histopatology of a bullous lesion from the leg reveals a  
157 subepidermal blister containing eosinophils, neutrophils and a mild mixed inflammatory infiltrate in  
158 the dermis (H&E 25X)