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Familial Interstitial Lung Disease in Children: Response to Chloroquine Treatment in One Sibling With Desquamative Interstitial Pneumonitis

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Summary. We describe a male infant with biopsy-confirmed interstitial lung disease (ILD) who responded to chloroquine, after he failed to improve on oral corticosteroids or cyclophosphamide. The infant presented at 8 days of age with respiratory distress and cyanosis. Lung biopsy at 8 weeks of age was consistent with desquamative interstitial pneumonitis (DIP). He was treated with corticosteroids at 2 weeks of age because of a family history of two siblings who died during infancy and who had DIP on postmortem examination. At 8.5 months, our patient was treated with cyclophosphamide because of lack of response to corticosteroids therapy. At 14 months of age, he began treatment with chloroquine in addition to corticosteroids and had a dramatic response within 3 weeks. The patient has been maintained successfully on continuous treatment with chloroquine alone for more than 9 years since this treatment was started. **Pediatr. Pulmonol. 1997; 23:55–61.** © 1997 Wiley-Liss, Inc.

Key words: chloroquine; desquamative interstitial pneumonitis; familial interstitial pneumonitis; infantile onset.

INTRODUCTION

Familial interstitial lung disease (ILD) in children has a high mortality.[1–4] Various systems of classification for ILD have been proposed.[5] Liebow et al.[6] described six categories of ILD based on histologic examination of lung biopsy specimens, and these authors were the first to describe desquamative interstitial pneumonitis (DIP) in 1965. In addition to alveolar wall thickening (the pathologic marker of ILD), DIP has two characteristic features: proliferation of type II alveolar cells and large mononuclear cells that are chiefly of macrophage origin lying free in the alveolar spaces.[7] Familial cases of DIP have been previously reported.[1–4,8–10]

We describe an infant with neonatal onset of ILD who had two siblings with the same condition; the siblings died and have been described previously.[2] All three children in this family presented during the neonatal period with respiratory distress, cyanosis, and (later) failure to thrive. The first two siblings (one male and one female) died. The clinical features and types of treatment used in the three affected siblings are summarized in Table 1. There were two additional unaffected siblings in this family. In the case described in this report the male infant had an uneventful antenatal and birth history and presented with respiratory distress and tachypnea at 8 days of age. Although therapy with corticosteroids was started at age 2 weeks (because of the family history), he failed to improve. After an unsuccessful response to a 6-week trial or cyclophosphamide, the patient had a beneficial response to chloroquine, which was begun at 14 months of age. The patient has been followed to 11 years of age and has continued on chloroquine therapy. The unique characteristics of both early-onset ILD and familial ILD are discussed.

CASE REPORT

A 4.4-kg white male infant born at term was hospitalized at the International Missionary Training Hospital, Drogheda, Ireland, at 8 days of age because of poor feeding, respiratory distress (respiratory rate of 60–80/min), and cyanosis. Clinical examination revealed hyperinflation of the chest with good air entry and no adventitious sounds. Arterial blood gas studies on room air revealed a pH of 7.286, PaO_2 of 60 mm Hg, $PaCO_2$ of 51 mmHg, bicarbonate of 24 mEq/L, and a base excess of 2.1 mEq/L. Chest radiographs showed hazy densities in both perihilar regions progressing to ground-glass ap-

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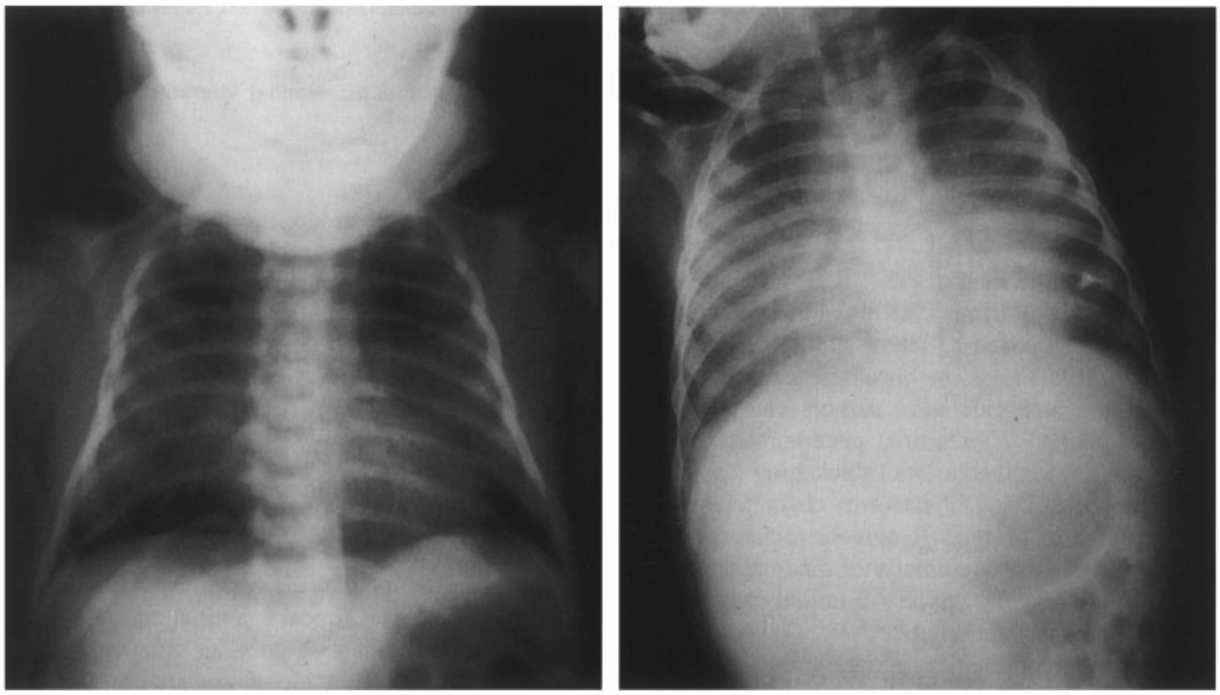
TABLE 1—Clinical Features of Three Siblings With Interstitital Pneumonitis

Feature	Sibling		
	1st	2nd	3rd
Date of birth	7/31/76	5/12/78	7/25/85
Sex	Female	Male	Male
Onset	3 wk	2 wk	1st wk
FTT[1]	Present	Present	Present
Clubbing	Absent	6 mo	12 mo
Cyanosis	Present	Present	Present
Therapy	Antibiotics Supportive	Antibiotics Corticosteroids from 3 mo[3] Azathioprine from 11 mo	Corticosteroids 2 wk[2] Cyclophosphamide 8.5 mo[2] Chloroquine 14 mo[2]
Outcome	Died at 7 mo of respiratory failure	Died at 22 mo of respiratory failure	Alive and well at 9 yrs
Time of diagnosis	Postmortem	Postmortem	8 weeks, open lung biopsy

[1]FTT, failure to thrive.
[2]Details are given in the text.
[3]Continued until death.



A B

Fig. 1. Chest radiographs. A: Hazy densities in both perihilar regions at 1 week of age. B: Progression of changes to near ground-glass appearance.

pearance (Fig. 1). Results of the following studies were within normal limits: sweat electrolyte test, serum immunoglobulins, α_1-antitrypsin, complement and antinuclear factor, and screening serology for toxoplasmosis, rubella, cytomegalovirus, and herpes.

Abbreviations

ILD Interstitial lung disease
DIP Desquamative interstitial pneumonitis

Because of a family history of ILD, prednisolone therapy was started at 2 weeks of age at a dosage of 2 mg/kg/day. Because there was no clinical improvement, the patient was transferred to the Hospital for Sick Children, London, U.K. for further investigations. Lung function tests revealed low-normal lung volumes, reduced

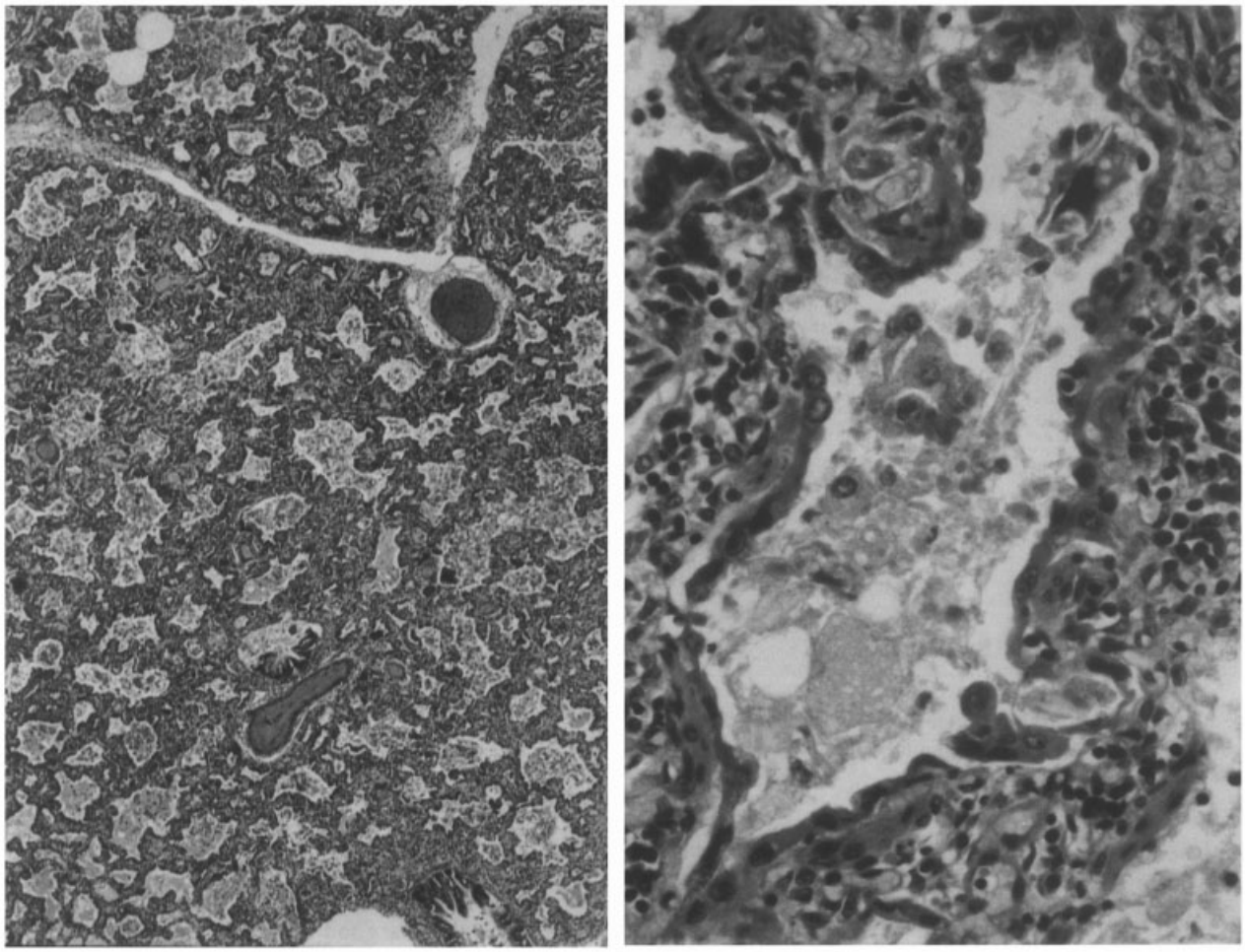


Fig. 2. Lung biopsy specimen at low power (A, ×25) and high power (B, ×400). Marked septal widening, type II alveolar epithelial hyperplasia, and increased accumulation of eosinophilic material and foamy macrophages within air spaces. (*A* and *B*, hematoxylin and eosin.)

compliance, and normal resistance consistent with restrictive lung diseases. Technetium perfusion/krypton scan showed no focal defects. An open lung biopsy was done at 8 weeks of age and showed marked alveolar septal widening, type II alveolar epithelial hyperplasia, and increased accumulation of eosinophilic material and foamy macrophages within the air spaces (Fig. 2). These findings confirmed ILD and suggested DIP. There were no bacterial pathogens or viruses isolated on lung biopsy. Indirect fluorescent antibody tests to respiratory syncytial virus, influenza A and B, adenovirus, and parainfluenza 1 or 3 were negative. The patient was transferred back to Drogheda within 2 weeks.

A 6-week course of cyclophosphamide at a dosage of 2.5 mg/kg/day was begun at 8.5 months of age because of a lack of response to corticosteroids. Respiratory distress and oxygen requirements continued to increase. Because of failure to improve with the addition of cyclophosphamide to the therapeutic regiment, chloroquine therapy was started at 14 months of age at a dosage of 10 mg/kg/day. There was a dramatic response within 3 weeks of starting this therapy. The respiratory rate dropped from the 80s to the 40s, and the oxygen requirement decreased from 4 L to 1 L/min. Two months later, a gradual taper of the corticosteroid dosage was initiated, and steroids were stopped at 30 months of age. The patient was discharged at 2 years of age.

At 3 years of age, the patient was receiving 70 mg of chloroquine daily (7 mg/kg/day). A reduction in chloroquine dosage by 2 mg/kg was attempted at this stage because of macular eye changes throught to be due to chloroquine; however, this resulted in reduced exercise tolerance and worsening of the chest radiographic findings. He was, thereafter, restarted on a daily dose of 70 mg, which was not changed despite increasing weight. At 9 years of age and on a dose of 70 mg/day (3.5 mg/kg/day), he is clinically asymptomatic with transcutaneous oxygen saturations of more than 95% at rest but has mild

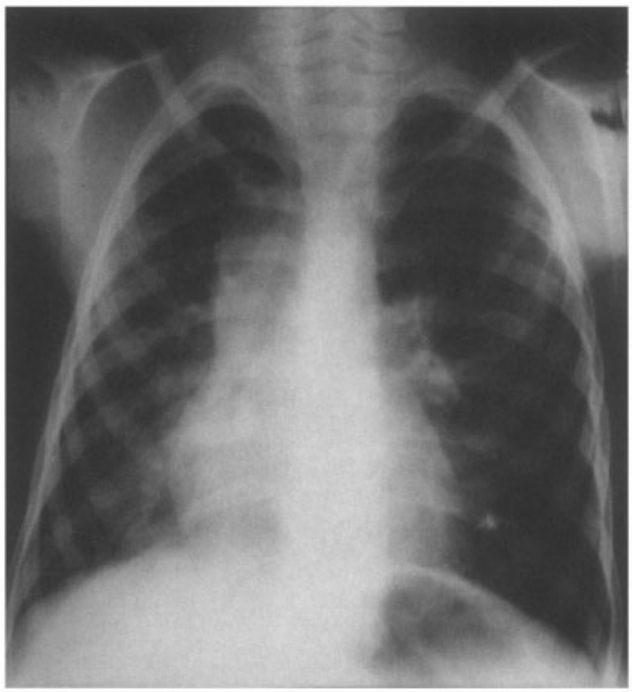


Fig. 3. Chest radiograph shows residual streaky densities, greater on right than left, with an interstitial pattern, which may in part represent fibrosis.

cyanosis on severe exertion. He has fine inspiratory crackles on auscultation. Chest radiographs continue to show significant changes bilaterally (Fig. 3).

DISCUSSION

There have been previous reports of familial interstitial pneumonitis.[1–3,8–15] The two siblings of the child described in this report have also been described previously.[2] Infants with familial interstitial pneumonitis become symptomatic in the first 6 weeks of life.[1–3] They have tachypnea and respiratory distress with grunting, intercostal and subcostal retractions, and cyanosis. The chest radiograph may show diffuse shadowing with an air bronchogram similar to that in neonatal respiratory distress syndrome. The diagnosis of ILD is confirmed by open lung biopsy.

The literature on DIP with onset at less than 1 year of age is summarized in Table 2. Hewitt et al.[16] reported seven infants with interstitial pneumonitis. Sharief et al.[15] reported 25 children, 15 of whom were younger than 1 year. A review of the literature found 20 case reports since 1970 (total of 42 infants) in which details on the patients were available; these are included in Table 2 and this report.[1–3,7–9,15–23] Stillwell et al.[10] reported 14 children, and 50% of them were younger than 1 year; however, this group was not included in Table 2 as the details of these cases were not available. In a review on chronic lung disease in 48 children, Fan et al.[4] described 4 (8%) who had DIP, but the age was not stated.

The familial occurrence of DIP has been previously described.[1–4,8–10] Among the case reports, the number of patients younger than 1 year of age was 20, and 10 had a positive family history (Table 2).[1–3,9] In a series of 25 children of all ages, 4 (16%) had a positive family history.[15] A positive family history was noted in 2 of 28 children in the series of Stillwell et al.[10] and in 2 of 7 in the series of Hewitt et al.[16]

Corticosteroids have been the mainstay of therapy for ILD. In general, a dosage of 2 mg/kg/day is recommended for oral use, to be continued until there is clinical improvement or for at least 8 weeks.[16,24] Of 38 patients treated, 18 were given corticosteroids alone, and the mortality rate was 55%. All seven infants in the series of Hewitt et al.[16] were treated with corticosteroids, and the mortality rate was 57%. Of 15 infants in the report by Sharief et al.,[15] 6 were treated with corticosteroids and 50% died. Among the 20 infants described in reports of one to four cases, 5 were treated with corticosteroids alone and 3 (60%) died (Table 2). These findings are in contrast to the previous belief that, in children, interstitial pneumonia is almost always a corticosteroid-responsive disease.[16] Kerem et al.[22] reported the use of intravenously administered methylprednisolone in three infants. One infant responded to a dosage of 15 mg/kg/day for 3 days on a monthly basis, given for 7 months; in the other two cases, methylprednisolone alone (10 mg/kg/day) failed to produce a good response, and other therapies were needed. Whether intravenous therapy has any advantage over oral therapy needs to be established. Among the reviewed cases reported here, six children received immunosuppressives, all in combination with corticosteroids—cyclophosphamide in three, azathioprine in two, and chlorambucil in one—without any benefit, and all of them died (Table 2).[1–3,19]

Chloroquine has been used successfully in the treatment of interstitial pneumonitis in childhood.[5] In the report by Sharief et al.[15] 6 of 15 infants were treated with chloroquine with or without corticosteroids and 1 child died. Among the 20 infants described in reports of one to four cases, 8 were treated with chloroquine, 7 in combination with corticosteroids. Two infants received chloroquine for less than 1 week before they died.[1,23] Of the remaining 6 patients, 5 survived and one died. Of 38 infants reported in Table 2 who received therapy, those treated with steroids alone had a mortality of 66% compared with 16% in those treated with chloroquine. In all the reports, chloroquine therapy was started at a dosage of 10 mg/kg/day. Among the 5 patients who responded, the response occurred within a month in all, within a week in two, and by 2 weeks in two.[7–9,21,22] Chloroquine was effective in four infants in whom corticosteroids were not effective, as in the case we describe

TABLE 2—Interstitial Pneumonitis During Infancy: Review of Case Reports Since 1970

Reference	Age at onset	Therapy[1]	Outcome	Comments
Hewitt et al., 1977[16]	Birth	st	Died 6.5 yr	
	8 days	st	Died 11 mo	
	Birth	st	Died 4.3 mo	
	Birth	st	Alive 5.5 yr	
	Birth	st	Alive 11.5 yr	
	Birth	st	Alive 3.3 yr	
	6 wk	st	Died 6 mo	
Sharief et al., 1994[15]	11 days	None	Alive	
	8 days	None	Alive	
	2 mo	None	Alive	
	3 mo	st	Alive	
	5 mo	st	Alive	
	6.5 mo	st	Alive	Poor response
	6 mo	st	Died	
	3.5 mo	st	Died	
	5 mo	st	Died	
	5 mo	chl	Alive	
	7 wk	chl	Alive	Poor response
	8 days	st, chl	Alive	
	11 wk	st, chl	Alive	
	4 wk	st, chl	Alive	Poor response
	1 wk	st, chl	Died	
Rosenow et al., 1970[17]	7 mo	st	Alive	
Howatt et al., 1973[18]	2 wk	st	Died 9.5 mo	
Barnes et al., 1975[19]	2 mo	st, aza	Died 9 mo	
Wigger et al., 1977[20]	1 mo	st	Died 3 mo	
Murphy and O'Sullivan, 1981[2] (one family)	3 wk[2]	None	Died 7 mo	
	2 wk[2]	st, aza	Died 22 mo	
Leahy et al., 1985[7]	Birth	st, chl	Alive	Maintained on chl, st not effective
Tal et al., 1984[1] (one family)	1 mo[2]	st, cyc	Died 3 mo	
	1.5 mo[2]	st, cyc	Died 3 mo	
	1.5 mo[2]	st, chl	Died 2 mo	chl less than 1 week
Farrell et al., 1986[9]	6 mo[2]	st, chl	Alive	Receiving therapy at 4 yr, st not effective
Springer et al., 1987[21]	2 mo	chl	Alive	No chl therapy at 4.5 yr
Buchino et al., 1987[3]				
Family 1	Birth[2]	st	Died 6 mo	
Family 2	1.5 mo[2]	st, cb	Died 3 yr	
	Birth[2]	st, cyc	Died 21 mo	
	Birth[2]	st, chl	Died 4 mo	chl used about 2 weeks
Karem et al., 1990[22]	3 mo	st, chl	Alive	st alone not effective
	2 mo	st	Alive	
Spencer and Price, 1991[23]	2 mo	st, chl	Died 3 yr	chl less than 1 week
Avital et al., 1994[8]	3 mo	st, chl	Alive 16 yr	No response to steroids, chl used for 7 months

[1]st, steroids; chl, chloroquine; aza, azathioprine; cyc, cyclophosphamide; cb, chlorambucil.
[2]Positive family history.

herein.[7,9,22] Two of the chloroquine-treated cases had recurrence of symptoms when the dose was tapered or therapy was stopped, which is similar to the experience in our case.[7,22]

Significant toxic effects involving the eye and other organs have been associated with long-term use of chloroquine and hydroxychloroquine. Hydroxychloroquine is safer than chloroquine for long-term use. Animal studies have shown that chloroquine may be 2 to 3 times more toxic than hydroxychloroquine.[25] Symptomatic corneal deposits or corneal edema occurred in about 50% of patients receiving chloroquine and in 0–10% of patients treated with hydroxychloroquine.[26] Retinopathic changes were observed in 10% of patients receiving long-term chloroquine therapy and in 3–4% of patients receiving hydroxychloroquine.[27] A dosage of 6.5 mg/kg/day or less, for less than 10 years, was not associated with any retinopathy in adults with arthritis who were treated with hydroxychloroquine.[28] The early retinopathy associated with chloroquine did not progress over a 5-year follow-

up once use of the drug was stopped.[26] In adults, use of the Amsler grid self-evaluation for a scotoma every 2 weeks was advised, and a careful ophthalmologic evaluation of visual fields every 6 months was recommended.[26,29]

In addition prolonged high-dose therapy with chloroquine may be associated with lichenoid skin eruption, blurring of vision, diplopia, bleaching of hair, T-wave abnormalities in the electrocardiogram, headache, and slight weight loss; all of these toxic effects are reversible on withdrawal of therapy. Other side effects include toxic myopathy, cardiomyopathy, and peripheral neuropathy; these are also reversible with discontinuation of drug therapy.[30]

The mechanism of action of chloroquine is unknown. Chloroquine and hydroxychloroquine belong to the 4-aminoquinoline family and are well known for their antimalarial and antirheumatic properties. Therapy with chloroquine was successful in a patient with idiopathic pulmonary hemosiderosis[31] and in another with lymphoid interstitial pneumonitis and decreased IgG and T-cell function without human immunodeficiency virus.[32] Also, two children who had acquired immunodeficiency syndrome with lymphoid interstitial pneumonia had a good response to chloroquine.[33]

In conclusion, ILD is rare in children. The clinical diagnosis may be difficult to establish in the early-onset cases. It requires a high degree of suspicion and needs to be confirmed by open lung biopsy. A positive family history of ILD may be present. The mortality rate is high, especially in children younger than 1 year. Corticosteroids and immunosuppressive agents are not very effective in this age group. The preliminary reports of cyclosporine therapy in older children and adults are not encouraging. The results with chloroquine are promising. Treatment with chloroquine should be considered early in the disease and should be used for an extended period of time. There are no reports of the use of chloroquine in adults; in children it has mostly been used as a second-line drug after treatment with corticosteroids and immunosuppressive agents. Multicenter trials of chloroquine therapy will be required to confirm its efficacy.

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