

The role of clinical and laboratory findings in the diagnosis of tuberculosis in pediatric patients: A 4-year single-center evaluation

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Submitted: 17.03.2024

Accepted: 29.07.2024

ABSTRACT

Objective: Early diagnosis of tuberculosis (TB) is important in reducing morbidity and mortality. In this study, we aimed to determine the signs and symptoms that provide the differential diagnosis of TB in pediatric patients.

Patients and Methods: The study included children diagnosed with TB between 2019 and 2023. Patients' clinical, laboratory, and radiological findings, treatments, clinical course, and complications were analyzed.

Results: Of a total of 28 patients, 15 had pulmonary TB, 6 had lymphadenitis, and 7 had abdominal TB. Their median age was 127.28±65.11 months; sixteen patients (57.1%) were male, and 11 (39.3%) had contact. Prolonged cough, fever, weight loss, and abdominal pain were the most common symptoms. Eighteen (64.3%) had a history of antibiotic usage. C-reactive protein and erythrocyte sedimentation were statistically significantly higher in patients with abdominal TB than patients with pulmonary TB, and lymphopenia and hypoalbuminemia were more common (0.009, 0.002, p<0.005), no inflammation sign in patients with TB lymphadenitis. Diagnosis was made by microbiological tests in 15 patients (53.6%), by clinical plus radiological findings in 11, and by response to the antituberculosis treatment in 2 patients.

Conclusion: Tuberculosis should be suspected in subacute infections with high inflammatory markers that do not improve with non-specific antibiotic treatment and abdominal involvement should be investigated in pulmonary TB.

Keywords: Tuberculosis, Children, Diaonosis, Abdominal, Extra pulmonary

1. INTRODUCTION

Tuberculosis (TB) is one of the top 10 infectious diseases that causes death worldwide. The causative agent is *Mycobacterium tuberculosis* (*M. tuberculosis*), which is transmitted through the respiratory route. Türkiye is a moderately endemic region for TB, and its incidence is 14 per 100,000 [1]. The difficulty of making a definitive diagnosis of TB in pediatric patients prevents the determination of real numbers for children. In its 2022 report, the World Health Organization (WHO) stated that approximately 1.3 million (12%) of the 10.6 million tuberculosis cases estimated in 2021 occurred in children under 15 years of age [2]. An exact number of children with TB is important since children acquire the infectious agent from adults, mainly their

household, caregivers, and teachers. An increase in the number of pediatric patients indicates that the disease is not under control.

M. tuberculosis typically affects the lungs, but it can also involve other organ systems, causing extrapulmonary TB, which causes a variety of already subtle symptoms of the disease that lead to a delay in diagnosis. Unfortunately, compared to adults, extrapulmonary TB is more common among children, especially in children under 5 years of age. Extrapulmonary involvement causes a challenge in diagnosis. The definitive diagnosis of TB in children can reach 75% in infants; this rate can be achieved in less than 50% of children with pulmonary TB diagnosed with

How to cite this article: Ocal-Demir S, Bozbeyoglu G, Celikel K. The role of clinical and laboratory findings in the diagnosis of tuberculosis in pediatric patients: A 4-year single-center evaluation. *Marmara Med J* 2025;38(1): 55-61. doi: 10.5472/marumj.1627948

clinical criteria [3]. History of recent contact with an infectious case, prolonged cough, fever, weight loss, and growth retardation are well-known warning symptoms for TB. It is important to know the symptoms and signs of extrapulmonary TB and their place, among other findings, in order to avoid delay in diagnosis. In this study, we aimed to determine the warning symptoms and findings that can be used for early diagnosis of TB by examining the data of all our patients diagnosed with TB, regardless of the area of involvement.

2. PATIENTS and METHODS

The study was approved by the Medeniyet University, Goztepe Prof. Dr. Suleyman Yalcin City Hospital, Clinical Researches Ethics Committee (approval number: 2023/0017, date: 25.01.2023).

Children aged between 0 and 18 who were diagnosed with tuberculosis and followed up in the Pediatric Infectious Diseases Clinic, Goztepe Prof. Dr. Suleyman Yalcin City Hospital, between July 1, 2019, and June 30, 2023 were included. The patient's medical files were reviewed retrospectively, and their ages, gender, admission symptoms, examination findings, laboratory data, radiological imaging, histopathological findings, treatments, clinical course, outcomes, and complications were noted in Excel files.

Statistical analysis

The IBM SPSS Statistics 22 program was used for statistical analysis. The suitability of the parameters for normal distribution was evaluated with Shapiro-Wilk tests, and it was determined that the parameters did not show normal distribution. In addition to descriptive statistical methods (minimum, maximum, mean, standard deviation, median, frequency), the Kruskal Wallis test (post hoc Dunn's test) and Mann-Whitney U test were used to compare the parameters between two groups in comparing quantitative data. Fisher Freeman Halton Exact test was used to compare qualitative data. Significance was evaluated at $p < 0.05$ level.

3. RESULTS

In the Pediatric Infectious Diseases Clinic, 28 patients were followed up during 4 years. Fifteen patients had pulmonary TB, seven had abdominal TB, and 6 had TB lymphadenitis (Figure 1). However, abdominal involvement was detected in three patients with pulmonary TB, and lung involvement was detected in four patients with abdominal TB. Abdominal TB consisted of one peritoneal, splenic, and five intestinal TB, mainly involving the ileocecal region. The ages of patients ranged from 4 to 216 months, with a mean of 127.3 ± 65.1 months (median 150 months); sixteen patients (57.1%) were male. Twenty-six patients (92.9%) had BCG vaccination, and the vaccination status of 2 patients was unknown. Eleven patients (39.3%) had a history of contact with an infectious case, and five patients (17.9%) were immigrants (Table I).

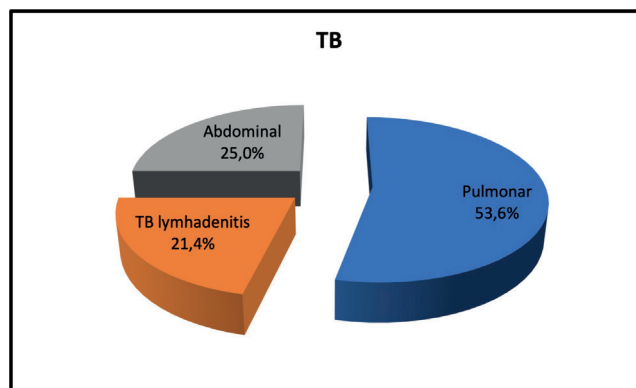


Figure 1. Distribution of tuberculosis type in children with tuberculosis

Table I. Demographic and clinical features of children with tuberculosis

Characteristics	N, frequency	%, percentage
Age (months)	127.3±65.1	
Gender, Male	16	57.1
Underlying disease	3	10.7
BCG vaccination	26	92.9
Contact	11	39.3
Immigrant	5	17.9
Symptoms		
Cough	15	53.6
Prolonged fever	14	50.0
Weight loss	8	28.6
Vomiting	8	28.6
Night sweat	7	25.0
Myalgia	6	21.4
Abdominal pain	6	21.4
Neck swelling	6	21.4
Dyspnea	5	17.9
Constipation	3	10.7
Rash	3	10.7
Diarrhea	2	7.1
Arthralgia	1	3.6
Hemoptysis	1	3.6
Physical examination		
Abnormal auscultation sound of lungs	13	46.4
Tachypnea	5	17.9
Abdominal tenderness	4	14.3
Splenomegaly	1	3.6
Lymphadenomegaly	13	46.4
Cervical	7	
Submandibular	4	
Axillary	1	
Inguinal	1	
Hepatomegaly	3	10.7
Hepatosplenomegaly	2	7.1
Splenomegaly	1	3.6

BCG: Bacillus Calmette-Guerin,

The symptoms of patients were cough (53.6%), prolonged fever (50%), weight loss (28.6%), vomiting (28.6%), night sweats (25%), and myalgia (21.4%), abdominal pain (21.4%), and neck swelling (21.4%). Eighteen patients (64.3%) had previously visited at least one health institution and used non-specific antibiotics without improvement. Frequently detected findings during the examination were abnormal lung auscultation (46.4%), lymphadenomegaly (46.4%), hepatomegaly and/or splenomegaly (28.6%), and abdominal tenderness (14.3%). Laboratory examinations revealed that 14 patients had anemia (50%), 20 had elevated C-reactive protein (CRP) (>5mg/dL) (71.4%), 18 had elevated erythrocyte sedimentation rate (ESR)

(>30 mm /hour) (64.3%) (Table II). There were no significant differences between patients with abdominal, pulmonary, and lymphadenitis TB regarding age and gender. In patients with abdominal TB, CRP and ESR were statistically significantly higher ($p:0.001$, $p:0.003$, respectively), and lymphopenia and hypoalbuminemia were statistically significantly more frequent ($p:0.009$, $p:0.009$) (Table III). Procalcitonin was measured in 17 patients and was above 0.5 ng/ml in 4 patients (23.5%); 3 had severe pneumonia-pleural effusion, and 1 had widespread ascites in the abdomen. Three patients were admitted to the Pediatric Intensive Care Unit (PICU). All patients were negative for anti-HIV.

Table II. Laboratory findings of children with tuberculosis

	n	Minimum	Maximum	Mean±SD	Median
White Blood Cell Count (WBC)	28	3400	25200	8866.43±4470.66	7995
Neutrophils	28	2150	22900	5911.07±4313.30	4990
Lymphocytes	28	400	5700	2360.00±1134.10	2455
Hemoglobin (Hg)	27	7.2	16.10	11.52±2.06	12
Platelet	28	208000	551000	348071.43±103705.04	341000
Aspartate aminotransferase (AST)	28	13	52	27.46±11.53	25,5
Alanine aminotransferase (ALT)	28	5	100	17.75±17.35	14
Creatinine	28	0.17	1.32	0.51±0.23	0.49
Blood urea nitrogen (BUN)	28	2.2	60	22.65±11.92	21,5
Albumin	27	2.74	4.84	3.94±0.60	4.05
C-reactive protein (CRP)	28	0.22	274.69	62.60±86.38	16.85
Erythrocyte Sedimentation rate (ESR)	27	2	120	59.85±41.41	51
Procalcitonin	17	0.03	100	9.24±26.26	0.122
Fibrinogen	12	72	1113	533.50±245.48	522.5
Adenosine deaminase (ADA)	4	68.3	185	112.05±54.67	97.45
Tuberculin Skin Test (TST)	22	0	24	10.27±8.40	12.5

Table III. Laboratory findings of patients according to types of tuberculosis

	Pulmonary (n=15) mean±SD (median)	Lymphadenitis (n=6) mean±SD (median)	Abdominal (n=7) mean±SD (median)	p
White Blood Cell Count (WBC)	8432±5041.48 (7900)	9196.67±2883.76 (8590)	9514.29±4757.6 (7100)	0.621
Neutrophils	5661.33±5047.53 (4710)	4891.67±2280.3 (4530)	7320±4053.23 (6380)	0.291
Lymphocytes	2389.33±682.04 (2500)	3423.33±1516.86 (3100)	1385.71±738.08 (1200)	0.009*
Hemoglobin	11.77±1.79 (12.3)	43.83±51.63 (13.1)	25.43±39.15 (10.6)	0.238
Thrombocytes	325066.67±94448.37 (329000)	367000±89605.80 (362500)	381142,86±133915.93 (368000)	0.397
Aspartate aminotransferase (AST)	24.2±10.2 (22)	29.17±10.87 (28)	33±13.86 (31)	0.149
Alanine aminotransferase (ALT)	18.6±23.05 (11)	14.33±1.03 (14)	18.86±9.96 (17)	0.247
Creatinine	0.47±0.14 (0.5)	0.49±0.22 (0,4)	0.64±0.34 (0,5)	0.474
Blood urea nitrogen (BUN)	22.27±10.64 (25)	19.33±4.63 (19)	26.31±18.18 (26)	0.739
Sodium	137.13±3.02 (138)	136.83±1.47 (136.5)	132.71±5.28 (134)	0.120
Albumin	3.75±1.19 (4.1)	4.41±0.25 (4.5)	3.39±0.37 (3,4)	0.009*
C-reactive protein (CRP)	40.91±64.41 (15,7)	4.63±5.69 (1.7)	158.75±92.46 (156,4)	0.001*
Erythrocyte Sedimentation rate (ESR)	50.64±38.29 (31.5)	28.33±24.21 (27)	105.29±12.85 (103)	0.003*
Procalcitonin	6.29±17.5 (0,1)	0.1±0.08 (0.1)	17.73±40.33 (1,1)	0.117
Fibrinogen	557.67±336.58 (569)	-	509.33±133.74 (493)	*0.522

Kruskal Wallis Test, *Mann-Whitney U Test * $p<0.05$

Chest radiography was taken in all patients, and varying degrees of radiological abnormalities were present in all patients with pulmonary TB and four of seven patients with abdominal TB. Chest X-rays of four patients showed only hilar/mediastinal fullness, 12 patients had infiltrations with/without hilar/mediastinal fullness, five had pleural effusion, four of which were

empyema, and three of which had cavitory lesions (Figure 2). Abdominal ultrasonography was performed in 18 of the patients (64.3%), and in 10, there were pathological findings: mesenteric lymphadenopathy (90%), thickening of the intestinal wall (70%), thickening of the peritoneum (50%) and hepatosplenomegaly (40%) (Figure 2.f).

Table IV. Clinical and laboratory findings of patients for the diagnosis of tuberculosis

Case	TB, type	Household Contact	TST (mm)	IGRA	AFB	Xpert MTB/RIF	Mycobacterial culture	Radiological findings	Histopathological findings
1	Pulmonary	+	10					Hilar mediastinal LAP	
2	Pulmonary		12			+	+	Hilar, axillar, mediastinal	
3	Pulmonary		0	neg			+	Hilar	
4	Pulmonary	+	0			+		Hilar	
5	Pulmonary		10	neg			+	-	
6	Pulmonary	+	NA				+	Mediastinal hilar, subcarinal	
7	Pulmonary	+	13	+				Left paratracheal	
8	Pulmonary	+	15	neg				Mediastinal LAP, infiltration	
9	Pulmonary	+	18					Hilar LAP, infiltration	
10	Pulmonary		0	neg				Hilar mediastinal LAP, infiltration	Granuloma
11	Pulmonary		NA				+	-	
12	Pulmonary	+	NA	neg				Miliary infiltration paratracheal subcarinal LAP	
13	Pulmonary		21		+	+	+		
14	Pulmonary		3	+					
15	Pulmonary and abdominal		0					Cavitory lesion in lung	
16	Pulmonary and abdominal	+	15			+	+	Hilar LAP	Non-specific
17	Pulmonary	+	20			+			
18	Abdominal		NA	+				Early stage cavitory lesion in lung	Non-specific
19*	Abdominal		NA					Ascites, inflamed intestine pulmonary infiltration	Non-specific
20	Abdominal		24			+		Inflamed intestine	Caseous necrosis
21	Abdominal		18			+	+	mesenteric inflamed intestine	Necrosing granuloma
22	Abdominal		0				+	Inflamed intestine	Necrosing granuloma
23	lymphadenitis		14	+					Caseous necrosis
24	lymphadenitis		NA						Necrosing granuloma
25	lymphadenitis		0		+		+	Axillar inguinal	Non-specific
26	lymphadenitis		20			+		Cervical-submandibular	Necrosing granuloma
27	lymphadenitis		0					Cervical	Non-specific
28	lymphadenitis		13			+		Cervical	Caseous necrosis

TB: Tuberculosis, TST: Tuberculin Skin Test, IGRA: Interferon gamma release assay, AFB: Acid-fast bacillus, Xpert MTB/RIF: Nucleic acid amplification (NAA) testing, LAP: lymphadenopathy, NA: non-applicable, Neg: negative

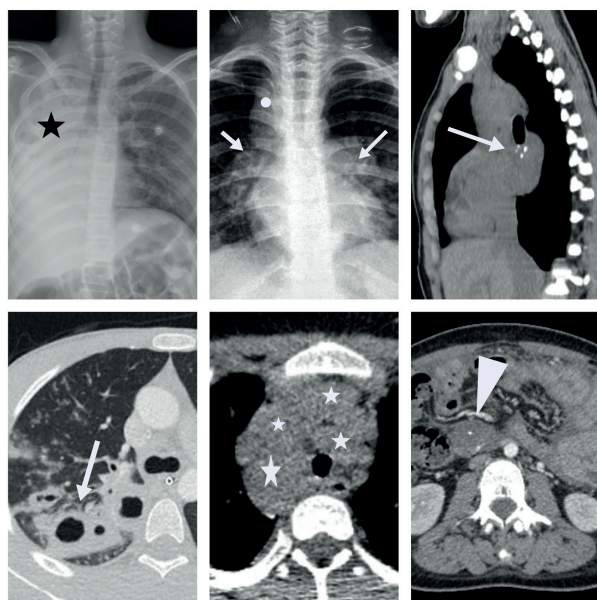


Figure 2. Radiological findings of children with tuberculosis
Pneumonia involving the entire right lung (asterisk) including cavitation and associated pleural effusion (a). White dot shows right paratracheal, white arrows shows hilar lymphadenopathy (b). Right hilar calcified (arrow) lymphadenopathy (c). TB pneumonia causing cavitation in the right lung (white arrow) and sometimes appearing like tree-in-bud (d). TB observed in right paratracheal, mediastinal (stars) and neck lymphadenopathies (e). TB with abdominal involvement, including right para-aortic calcified (arrowhead) LAP, free intra-abdominal fluid and peritoneal thickening (f).

Tuberculin skin test (TST) was performed in 22 patients; its diameter was ≥ 15 mm in eight, 10-14 mm in six, 3 mm in one, and 0 mm in seven patients. Interferon-gamma release assay (IGRA) was positive in one patient who did not undergo TST and another one with a TST of 3mm (Table II). Gastric aspirate, sputum, tissue, and pleural or peritoneal specimens were obtained and sent to be examined for acid-fast bacilli smear (AFB), mycobacterial culture, and molecular test (Xpert MTB/RIF). In 15 of 28 patients (53.6%), a definitive diagnosis could be made with microbiological examinations; in five of them, mycobacterium grew in culture; in five, only Xpert MTB/RIF was positive; in three, mycobacterium grew beside Xpert MTB/RIF positivity, in two AFB and Xpert MTB/RIF were positive and bacteria grew in culture. Mycobacteria grew in the mycobacterial culture of gastric aspirate of three patients hospitalized due to severe pneumonia and empyema. They had a late one-month after admission and partial clinical response to non-specific antibiotic treatment. The histopathological study was performed in 15 patients, 10 from lymph nodes and five from intestinal biopsy. The results were reported as non-specific in five cases, necrotizing granuloma in four, granuloma with caseous necrosis in three, and granuloma in three cases (Table IV).

Treatment was initiated after diagnosis of TB except for two patients, one with severe ascites and one with lymphadenitis, who were unresponsive to non-specific antibiotic treatment;

antituberculosis treatment was started empirically. Their fever decreased within the first week, and inflammation markers decreased in the second week, but they finally responded fully to this treatment. At the beginning of treatment, one patient developed hepatotoxicity, and one developed acute renal failure. All antituberculosis drugs were discontinued until the liver and renal function tests returned to normal range. After one week, treatment was restarted with the same drugs; treatment was completed without any problem.

4. DISCUSSION

Diagnosis of TB is challenging because of its subacute course with mild symptoms. In our study, the average time until patients were diagnosed was 2.6 months. Although, there is no clear information in the literature about the duration of diagnosis of pediatric tuberculosis, this period was reported as 4 months in the study of Sadhna et al., in which they examined 218 patients with abdominal TB [4]. This longer diagnosis time in their study may be related to the fact that abdominal tuberculosis has vague symptoms. Another reason may be the significantly different size of study samples. Preventing delay in diagnosis is possible by performing clinical, laboratory, radiological, microbiological, and sometimes histopathological diagnostic examinations and analyzing the findings together.

A history of close contact with infectious cases is important in the diagnosis of tuberculosis. In fact, even if an adult patient is AFB negative, he or she can infect 30-40% of the child contacts at home [5]. In our study, 39.3% of our patients had a contact history. Being an immigrant is another important risk factor for migrating from an endemic area or living in unfavorable conditions. The number of immigrants in our patient group was also remarkable.

The most common symptoms at the admission of our patients were prolonged cough, fever, weight loss, vomiting, night sweats, abdominal pain, and neck swelling. The reason for this diversity in symptoms may be that TB symptoms are not specific and that all patients diagnosed with TB, regardless of the location of involvement, were included in the study. Mulenga et al., in their study, included 1017 infants with pulmonary tuberculosis (HIV negative) from South Africa and found that 64% of the patients were symptomatic. The most common symptoms were growth arrest (50%), prolonged cough (17%), and wheezing (13%); compared to our study, their patients had less weight loss (3%), fever (2%), and lethargy [6]. During the evaluation of the patient for TB, in addition to questioning classic symptoms such as prolonged cough, fever, and weight loss, also questioning symptoms indicating extrapulmonary involvement, such as abdominal pain, vomiting, change in bowel habits, muscle pain, and lymph node enlargement will increase the chance of early diagnosis. The abdominal TB symptoms in our patients were vague; patients with TB lymphadenitis had no systemic symptoms or signs; the reason for their admission was lymphadenomegaly, which did not improve with non-specific antibiotics. The fact that more than half of our patients had previous hospital admissions and had used non-specific antibiotics and did not

recover shows that TB should be considered in the differential diagnosis of infectious diseases that do not respond to non-specific antibiotics.

Laboratory tests of patients with TB revealed anemia and elevated CRP and ESR levels, which are inflammatory markers. When TB types were compared with each other in terms of inflammatory markers, CRP and ESR values were significantly higher, and hypoalbuminemia and lymphopenia were significantly more frequent in abdominal TB than in pulmonary TB. It has been reported that 50-80% of patients with abdominal TB have mild anemia and increased ESR with normal white blood count [7]. Since, routine laboratory tests are not differential in diagnosing TB, more specific tests such as TST, IGRA, microbiologic, and histopathologic tests can be used. In this study, TST was over 15mm in 36.4% of our patients, all of whom were vaccinated with BCG, and over 10 mm in 63.4%. This situation suggests that in our moderately endemic country where BCG vaccination is applied, values in the 10-15mm range should be interpreted carefully in the presence of clinical suspicion. The sensitivity of TST in diagnosing TB is 67-85%; the sensitivity of IGRA is similar (57-85%), but its specificity is higher (85-100%) [8-11]. Among the microbiological tests studying AFB, mycobacterial culture and Xpert MTB/RIF increased the possibility of diagnosis by approximately 3 times compared to studying either alone in this study. Although, Xpert MTB/RIF testing is not valid for gastric aspirate, its positivity was compatible with the patient's clinical and microbiological findings. Culture growth has been reported to be lower than 40% in children due to the disease containing few bacilli in pediatric patients [12]. A definitive diagnosis could be made with microbiological tests in only slightly more than half of our patients; the diagnosis could not be made until empiric treatment started in two patients.

Abdominal TB is a rare type that accounts for 5% of all cases of TB worldwide [13]. It is thought that because of its vague, non-specific symptoms, it is not diagnosed and reported adequately. Abdominal involvement was reported in 37.5% of autopsies of children who died due to pulmonary TB [14]. TB intestinal types are assumed to develop when a patient with pulmonary TB swallows' sputum-containing bacilli [15,16]. In our study, lung involvement was demonstrated in four of our seven patients with abdominal TB by radiological evaluation, and in two of them, Xpert MTB/RIF positivity was detected. On the contrary, in three patients with pulmonary TB, abdominal TB findings were detected on ultrasound. So, when investigating TB, anamnesis, examination, and test planning should be done for other areas of involvement, such as the abdomen and pulmonary TB.

The limitations of this study were due to its retrospective design. This design prevented us from including patients whose data we could not access in the study, so the sample size remained small, and the results obtained from the study could not be generalized.

Conclusion

Early diagnosis of TB is based on physician suspicion and often requires analysis of more than one parameter. In addition, TB should be investigated in subacute infections with elevated inflammatory markers that do not improve with non-specific

antibiotic treatment. Extrapulmonary TB should not be forgotten in pediatric patients, especially abdominal, which is frequently associated with pulmonary TB.

Compliance with Ethical Standards

Ethical approval: The study has been approved by Medeniyet University, Goztepe Prof. Dr. Suleyman Yalcin City Hospital, Clinical Research Ethics Committee (decision no: 2023/0017, date: 25.01.2023).

Conflict of interest: The authors declare that they have no conflict of interest.

Financial support: The authors declare that they have no financial support.

Authors contributions: All authors contributed to the study's conception and design. SOD, GB and KC: Material preparation, data collection and analysis, SOD: Writing the first draft of the manuscript. All authors read and approved the final manuscript.

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