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Clinical characteristics, complications and prognosis of seventy-nine measles cases

Yetmişdokuz kızamık olgusunda klinik özellikler, komplikasyonlar ve prognoz

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Aim: To investigate the age distribution, clinical presentations, laboratory and radiological findings, complications and prognosis of measles in children.
Materials and Methods: The children with the clinical diagnosis of measles which was confirmed by a sensitive enzyme immunoassay for measles IgM antibody were evaluated comprehensively aspect to complication of measles (i.e. pneumonia, otitis media, encephalitis).
Results: The ages of the 79 patients with measles ranged from 1 to 180 months. The severity of the disease was significantly correlated with the younger age ($p<0.001$), higher levels of blood neuthrophil counts and serum C-Reactive Protein (CRP) ($p<0.05$). The most common complications were pneumonia (75%) and encephalitis (9%). Three (3,8%) patients died due to the complications.
Conclusion: It was found that the severity of measles and the rate of complications are high especially in infancy. Secondary bacterial pneumonia is the most common complications and also responsible for the severity of measles. Acute measles encephalitis is not infrequent. Infancy, very severe pneumonia, malnutrition and compromised immunity are the major factors which increase mortality.

Key words: ***measles, children, complications***

Amaç: Kızamığın çocuklarda yaş dağılımını, klinik ve laboratuar özelliklerini, radyolojik bulgularını, yan etkilerini ve prognozu değerlendirmek amaçlandı.
Gereç ve Yöntem: Klinik olarak kızamık tanısı konulan ve kızamık IgM antikor mikroELISA yöntemi ile de tanısı kesinleşen olgular kızamığın yan etkileri (alt solunum yolu enfeksiyonu, orta kulak iltihabı, ensefalit) açısından ayrıntılı olarak değerlendirildi.
Bulgular: Yetmiş dokuz olgunun yaşları 1–180 ay arasında değişmekteydi. Hastalığın şiddeti yaşın küçük olması ($p<0.001$), kan nötrofil sayısındaki ve CRP'deki yükseklik ile ($p<0.05$) ciddi olarak ilişkili bulundu. En sık görülen yan etki pnömoni (%75) ve ensefalit (%9) idi. Üç (%3,8) olgu kızamık yan etkilerinden dolayı kaybedildi.
Tartışma: Özellikle bebeklik dönemindeki çocukların, kızamığın şiddeti ve yan etkileri açısından daha duyarlı oldukları saptandı İkincil bakteriyel alt solunum yolu enfeksiyonu oldukça sık ve ayrıca hastalığın ciddiyetinden sorumlu faktör olarak saptandı. Akut kızamık ensefalitinin de düşünüldüğü kadar ender olmadığı görüldü. Bebeklik dönemi, çok ciddi alt solunum yolu, malnütrisyon ve immun baskılanma mortaliteyi artıran büyük risk faktörleri olarak saptandı.

Anahtar sözcükler: ***kızamık, çocuk, yan etkiler***

Measles is a highly contagious acute viral illness characterized by a distinct exanthem, pathognomic enanthem, accompanied by the classical triad of cough, coryza and conjunctivitis (1). Measles immunization is highly effective in preventing measles and reduces mortality in immunized children by 40-75% (2). The first measles vaccination is given to infants at 9th months according to the Ministry of Health's recomendations in Turkey. Measles related deaths account for about 10% of all deaths in children under the age of 5 years in developing countries (3). Acute measles infection at an early

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age is associated with more complications and increased mortality (4). The most important complications of measles which cause morbidity and mortality are bronchopneumonia, otitis media, diarrhea, croup and encephalitis (1, 5, 6). Pneumonia complicates measles as many as 80% of all cases and is responsible for 25 to 100% of measles deaths in developing countries. Measles is responsible for 6 to 21% of all cases of acute lower respiratory infections and 8 to 50% of all pneumonia-associated deaths in developing countries (7). Measles is a severe illness in immuno-compromised patients (8).

In this study we investigated the age distribution, clinical presentations, laboratory and radiological findings, complications and prognosis of measles in patients who were referred to Dr. Sami Ulus Children's Hospital between 1st January 2001-31th December 2001 during a measles outbreak in Turkey.

Material and Methods

All followed children in Dr. Sami Ulus Children's Hospital as outpatients or inpatients, who had positive measles IgM antibody, with the clinical diagnosis of measles were enrolled into the study during the year of 2001. Measles was clinically considered as the presence of fever, exanthem and Koplik's spots. All patients, except one, had typical clinical picture of measles.

The demographic characteristics, contact history with the measles patients (within 3 weeks), vaccination status, clinical symptoms and physical findings of the patients were recorded on standart forms.

The pneumonia was diagnosed as a result of tachypnea and abnormal chest X-ray. The patients who had pneumonia complication were graded according to the protocol defined by the World Health Organization (9). The diagnosis of encephalitis was based on the presence of altered degree of conciousness, convulsions and lymphocytic pleocytosis in cerebrospinal fluid (CSF) and / or electroencephalography (EEG) findings (10, 11). Chest radiographies were taken routinely even in the absence of respiratory symptoms. Radiographic interpretations were made by a radiologist.

Vitamin A was given to all patients who had pneumonia at dose of 200.000 IU on consecutive two days.

Blood gases values, hemoglobin (Hb) levels, peripheral blood leukocyte, neuthrophil, platelet counts, erythrocyte sedimantation rate (ESR), serum C-Reactive Protein (CRP), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) measures of the patients were recorded.

Blood Culture: Blood cultures of the patients were taken at admission. For blood culturing automated system was used (Organon Tecnica BacT Alert) when the presence of growth is signalled, subculturing is performed to blood agar and EMB agar.

Measles Antibody Test: The test is based on the principle of the capture of the immunoglobulins and subsequent identification of those which are specific making use of their ability to bind an antigen conjugated to peroxidase. The capture is performed using monoclonal antibodies bound to solid phase (microtiter wells). The antigen is composed of purified, inactivated measles virus.

Fresh or defrosted serum samples were stored at 2-8 C° for 5 days. Samples were diluted 1/101. Then distribution, incubation, washing, adding immunocomplex, adding substrate and stop solution were made automatically with Labotech automated microELISA system using Biochem Immunosystems Italia S.P.A.

Statistical Methods: Statistical analysis was carried out with SPSS Release 10.0.1. Pearson correlation analysis was conducted to determine whether the severity of measles related to age, peripheral blood neuthrophil counts, serum CRP levels, ESR's and fever. A logistic regression model was constructed to evaluate the main variables that could explain the severity of illness. The dependent variable was the severity of illness, and the independent variables were patient's age, fever, peripheral blood leukocyte count, neuthrophil count, ESR and CRP.

Results

The ages of the 79 patients with measles ranged from 1 to 180 months with a median of 36 months. Twenty-one patients (26.6%) were 1-9 months old, 14 patients (17.7%) were 10-24 months old, 16 patients (20.2%) were 25-60 months old, 19 patients (24%) were 61-120 months old, 9 patients (11.4%) were 120-180 months old. The age distribution of patients is given in Figure 1. Thirtynine (49.4%) patients were male.

Measles vaccine history among infants over 9 months (except younger than 9 months) was 46.5%. None of the patients received two doses of measles vaccine.

Forty-five (57%) patients had contact history with an other measles patient. The lowest age of patients was one month of age, had a recent history of her mother's measles.

During the study period, the monthly distribution of measles cases ranged between 0 to 22%. The peak occurence was from March to July (Figure 2).

The duration of the symptoms ranged from one to 15 days with a median of 5 days. The most frequent symptoms were cough, conjunctivitis and rhinore. The body temperature of the patients ranged from 35.7 C° to 40.0 C° with a median of 37.9 C°. The most frequent clini-

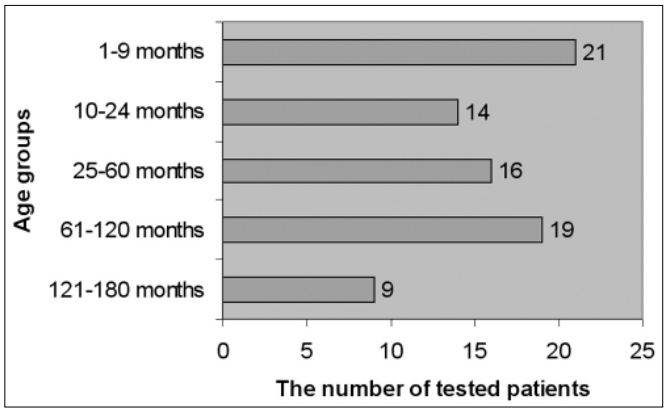

Figure 1. Age distribution of measles cases (n = 79).

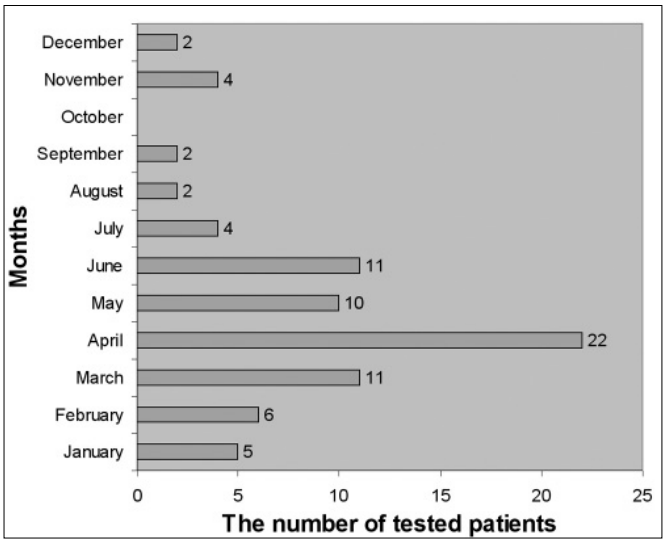

Figure 2. Dstribution of patients by monts.

cal findings were tachypnea, chest indrawing and cyanosis. The symptoms and clinical findings of the patients are summarized on Table 1.

Complications were detected for 73 (92.4%) patients. The most frequent complication was pneumonia (75%). The proportion of patients with complication except for otitis media was 100% among patients 1-9 months old, 92.8% among patients 10 to 24 months old, 81.2% among patients 25 to 60 months old, 63.1% among patients 61 to 120 months old and 77.8% among patients 121 to 180 months old. Younger patients were more severely ill ($p = 0.000$, $r = -0.514$). The second common complication was encephalitis. All 7 patients had depressed level of consciousness and convulsions. The other presenting finding was nuchal rigidity. Cerebrospinal fluid analysis showed lymphocytic pleocytosis and normal or mildly raised protein levels. Electroencephalography (EEG) showed diffuse slow activity. Only four patients were evaluated with computerized tomography revealing mild cerebral oedema in two of them. All showed good recovery without sequelae.

Table 1. Complications and clinical features in measles

Findings	*The number of tested patients (n = 79)*	%
Complications		
Pneumonia	59	74.6
Severe pneumonia	12	15.2
Very severe pneumonia	30	38
Otitis media	7	8.9
Encephalitis	7	8.9
Clinical symptoms / findings		
Rhinore	39	49.4
Conjunctivitis	57	72.2
Cough	77	97.5
Diarrhea	19	24.1
Vomiting	26	32.9
Decreased consciousness	10	12.7
Convulsion	7	8.9
Tachypnea	46	58.2
Chest indrawing	41	51.9
Cyanosis	27	34.2
Stridor	2	2.5
Wheezing	6	7.6
Stomatitis	6	7.6

Fifty-nine (74.7%) patients were hospitalized, 20 (25.3%) patients who were diagnosed followed-up as outpatients. Hospitalization period ranged from 3 to 61 days, with a median of 8.5 days. The patient who had been hospitalized for 61 days had Down syndrome and tuberculosis.

Pulmonary infiltrates were present radiographically in 44 (56.8%) patients, 13 patients had multiple radiological findings.

Blood gases analysis were made in 53 (67.1%) patients. The most common abnormality was hypoxemia (56.5%).

The hemoglobin, leukocyte, neuthrophil, platelet counts, ESR, CRP, AST and ALT measures of measles patients are summarized on Table 2 and Table 3. There was statistically significant correlation with disease severity and higher leukocyte counts, higher neuthrophil counts and higher serum CRP levels ($p = 0.000$, $p = 0.004$, $p = 0.014$ respectively, $r = 0.391$, $r = 0.309$, $r = 0.262$ respectively). A logistic regression analysis was done for factors that shown significant correlation with disease severity. It was established that: disease severity = 1.756 + (- 0.01 x patient's age [months] + (0.0049 x CRP) + (0.000034 x leukocyte count [/ mm^3]) ($p = 0.034$). There was no patient with clinical hepatitis among patients with increased liver enzymes.

Blood culture was examined in 56 (70.9%) patients and decided as positive in 4 (5.1%) patients: in one patient who had lobar pneumonia *S. pneumoniae*, in two

Table 2. Laboratory findings in measles

Finding	*Count*	*Minimum*	*Maximum*	*Median*
Hemoglobin (g / dl)	79	6.9	16	10.9
Leukocyte / mm3	79	2200	46.000	8900
Neutrophil / mm3	79	1040	38.640	4650
Platelet / mm3	79	1000	768.000	271.000
ESR (mm / hour)	78	5	140	30
CRP (mg / dl)	78	< 3.5	221	25.9
AST (U / L)	61	21	400	51
ALT (U / L)	61	3	206	24

Table 3. Laboratory findings in measles

	The number of tested patients	%
Leukocyte / mm^3		
≤ 5000	19	24
5000-15.000	47	59.5
≥ 15.000	13	16.5
Platelet / mm^3		
< 100.000	2	2.5
ESR (mm / hour)		
≤ 30	40	51.3
> 30	38	48.7
CRP (mg / dl)		
< 20	33	42.3
20-40	15	19.2
> 40	30	38.5
AST (U / L)		
< 60	43	70.5
> 60	18	29.5
ALT (U / L)		
< 45	47	77
> 45	14	23

patients *S. viridans* and in one patient *S. aureus* are isolated. Respiratory syncytial virus (RSV) and Adenovirus were detected serologically in one patient aged 6 years who developed bronchial hyperreactivity. During the course of measles, suspected pulmonary tuberculosis was diagnosed in 3 patients due to pleural effusion with lymphocytic pleocytosis and intrathoracal lymphadenopathy whose diameter > 10 mm.

Three (3.8%) patients died as a result of measles complications: one child aged 3 years had an underlying malign disorder and postmortem diagnosis of giant cell pneumonia, one child aged 6 months developed very severe pneumonia and respiratory failure, one child aged 6 months who had malnutrition developed very severe pneumonia, pneumothorax and respiratory failure.

Discussion

In this hospital-based study during a measles outbreak, age distribution showed that 35 (44%) of the cases were infants and the median age was 36 months. Twenty-one of cases were below 9 months of age, the recommended age for measles vaccination in Turkey. More than one-half of the patients had contact history with another measles patient. In developing countries high birth rates and high contact rates combined with early decrease of maternal antibodies result in high incidence of measles, during the first year of life (12, 13, 14). It was demonstrated that the ratio of children with detectable antibodies declined from 61.4 percent at 22-23 weeks of age to 20 percent at 26-27 weeks of age in Turkey (15). Ministry of Health reported a negative measles antibody incidence of 39.5% among subjects who 6 months-1 years old, 47% among 1-5 years old, 7.5% among 6-10 years old and 6% among > 10 years old, from rural and urban areas of three cities from Turkey during 2000-2001 (16). In developing countries where measles incidence is high, infants are at greater risk of being exposed to wild type measles virus shortly after maternal antibodies have waned (4). It has been suggested that, measles infection between 6 and 9 months of age remains a problem in some areas as a result of moderate vaccine coverage with one dose given after 9 months (12).

Measles vaccine coverage among infants over 9 months was 46.5%. It was reported that vaccine effectiveness is expected to be at least 85% when measles vaccine in administered at 9 months of age, but cold chain and other programme failures have reduced effectiveness in rural and urban areas in developing countries (17). Although there was two doses vaccination programme of Ministry of Health more than half of our patients did not receive measles vaccine. Second dose measles vaccination was introduced into the Turkey Expanded Program of Immunization in 1998. Mild illness of the infants may be cause to delay in immunization as wrongly. World Health Organization (WHO) recommends that to use all opportunities to immunize children (17).

Seventy-three (92%) of our patients had complications. We think that this high percentage of complications with measles is due to the referrel of complicated cases to our hospital. Dr. Sami Ulus Children's Hospital in Ankara, is a referrance center for patients with severe and complicated diseases from Ankara and the complicated cases from the rest of the country may be referred to our unit.

The most common complication was pneumonia (75%). In another hospital-based study during a measles outbreak, measles complications occured 82% of the children, most being pneumonia (18). A community-based

study during a measles outbreak, among 283 patients measles related complications were reported in total 31.1% cases, diarrhoea in 15.2% and pnemonia in 7.1% (19). In a recent study about measles epidemic in The Netherlands 1999-2000; 16% complication rate was reported among 3292 cases. The most frequent complications in this study were otitis media and pneumonia treated at home (20). In this epidemic, postmeasles pneumonia was reported as 33% (21).

The risk of more severe pneumonia was inversely related to age as reported other studies from developing countries (6, 18, 22). According to Centers for Disease Control (CDC), complications were reported one-third of infected children younger than 5 years of age. Of the 89 measles-related deaths at 1990, 55% occured in children younger than 5 years old (23).

Measles virus-associated pneumonia can be caused by the measles virus itself, as well as by other viruses and by bacteria (7). Interstitial pneumonitis due to measles virus replication in the lower respiratory tract is common in uncomplicated disease but it is usually clinically insignificant. Our patients had clinically apperent pneumonia with tachypnea (58.2%), chest indrawing (51.9%), cyanosis (34.2%), radiological infiltrates (56.8%) or more than one radiological findings (17%), hypoxemia (56.5%) and respiratory acidosis with or without hypoxemia (9%).

Measles was recognized to cause substantial morbidity and mortality due to secondary infections. Both disruption of mucosal surfaces and the immunosuppression associated with measles virus predispose to secondary infection, which is thought to occur in over half of children with measles associated pneumonia (2, 24, 25). We found that the disease severity was associated with the higher peripheral leukocyte, neuthrophil counts and higher serum CRP levels. This finding is suggests that disease severity was associated with secondary bacterial infections. However, in our study there were only 5.1% blood culture positivity. It had been reported that similary, 10 of the 182 (5.5%) measles patients had blood culture positivity. Authors suggested that the widespread practice in Philiphines of antibiotic use without prescription contributes to the low yield of blood cultures (7). It is known that persistent fever is an indication of complications at about 5th. day (1). We think that the 5 days of median duration of symptoms at admission in our study, could be support the presence of secondary bacterial pneumonia most of the cases.

In the study which investigated coinfections with measles-associated pneumonia, in 60 of 182 measles patients another viral pathogen was detected and in 35 cases there were 2 or more. The most common concominant virus was parainfluenzae virus, followed by adenovirus (7). We did not investigate concominant viral infection routinely, but one patient with bronchial hyperreactivity as a complication of measles had RSV and adenovirus IgM antibody.

Tuberculosis was also present in three measles patients. Investigators suggested that long-term inhibition of IFN-δ-driven IL–12 expression may have direct relevance to disease due to Mycobacterium tuberculosis, a pathogen classically associated with measles-induced exacerbations (25).

Nine percent of our measles patients presented with acute encephalitis. Acute measles encephalitis, presents as a recrudescence of fever during convalescence from measles, headaches, seizures and change in mental status (26).

It has been reported that hepatitis is an uncommon and ill-defined complication of measles (27). We found that increased hepatic enzymes during course of measles is not rare, but does not a clinical hepatitis and is transient.

We used vitamin A for the complicated measles patients as recommended by WHO (23). But we did not investigate its beneficial effects in this study.

Two of the deaths were due to very severe pneumonia in infants at 6 months of age. One of them was malnourished. Other investigators also demonstrated, the majority of deaths (52.5%) occur among 6-to–12-month old children (4). One of the deaths in our study had also ALL and giant cell pneumonia without rash. Measles is a severe illness in immunocompromised patients and absence of rash is frequent (8, 28, 29). The incidence of measles among children with cancer has been estimated at about 4%, mortality ranging from 29% to 83% (26).

In our study, we found that especially in infancy the severity of measles and the rate of complications are high. Secondary bacterial pneumonia is the most common and also responsible for the severity of measles. Acute measles encephalitis is not infrequent complication. Infancy, very severe pneumonia, malnutrition and compromised immunity are the major factors which increase mortality.

References

1. Maldonado YA. Rubeola virus (measles and subacute sclerosing panencephalitis). In: Long SS, Pickering LK, Prober LG (eds), Principles and Practice of Pediatric Infecrious Diseases. 2nd. edition. Churchill Livinstone Inc. 2003pp; 1148-1155.
2. Smyth A. Pneumonia due to viral and atypical organisms and their sequelae. Br Med Bull 2002; 61:247-262.
3. Chalmers I. Why we need to know whether prophylactic antibiotics can reduce measles-related morbidity. Pediatrics 2002; 2: 312-315.
4. Hartter HK, Oyedele OI, Dietz K, et al. Placental transfer and decay maternally acquired antimeasles antibodies in Nigerian children. Pediatr Infect Dis J 2000; 19:635-641.
5. Ibrahim SA, Mustafa OM, Mukhtar MM, et al. Measles in suburban Khartoum: an epidemiological and clinical study. Trop Med Int Health 2002; 5:442-449.
6. Marufu T, Siziya S, Tshimanga M, et al. Factors associated with measles complication in Gweru, Zimbabwe. East Afr Med J 2001; 3:135-138.
7. Quiambao BP, Gatchalian SR, Halonen P, et al. Coinfection is common in measles-associated pneumonia. Pediatr Infect Dis J 1998; 17:89-93.
8. Kaplan LJ, Daum RS, Smaron M, et al. Severe measles in immunucompromised patients. J Am Med Assoc 1992; 267:1237-1241.
9. Acute respiratory infections in children: case management in small hospitals in developing countries. Programme for the control of ARI. Geneva: World Health Organization, 1988.
10. Gunaratne PS, Ranjendran T, Tilakaratne S. Neorological complications of measles. Ceylon Med J 2000; 2:48-50.
11. El-Far F, Sztajnbok J, Marotto PC, et al. Meningoencephalitis in the acute phase of measles. Report of 6 cases. Arq Neuropsiquiatr 2000; 58:136-140.
12. Kaninda AV, Legros D, Jatau M, et al. Measles vaccine effectivenes in standart and early immunization strategies, Niger, 1995. Pediatr Infect Dis J 1998; 17:1034-1039.
13. Caceres VM, Strebel PM. Factors determining prevalence of maternal antibody to measles virus throughout infancy: a review. Clin Infec Dis 2000; 31:110-119.
14. Gans H, Yasukawa L, Rinki M, et al. Immune responses to measles and mumps vaccination of infants at 6,9, and 12 months. J Infect Dis 2001; 184:817-826.
15. Kanra G, Ceyhan M: Elimination of maternal antibodies against measles. Turk J Pediatr 1991; 33:217-220.
16. Epidemiyoji Ünitesi, Viroloji Laboratuvar Şefliği. Yapılan saha çalışmalarındaki kızamık antikor dağılımları. AER 2002; 1:11.
17. Akramuzzaman SM, Cutts FT, Hossain MJ, et al. Measles vaccine effectiveness and risk factors for measles in Dhaka, Bangladesh. Bull WHO 2002; 80:776-782.
18. Mgone JM, Mgone CS, Duke T, et al. Control measures and the outcome of the measles epidemic of 1999 in the Eastern Highlands Province. P N G Med J 2000; 43:91-97.
19. Thakur JS, Ratho RK, Bhatia SP, et al. Measles outbreak in a Periurban area of Chandigargh: need for improving vaccine coverage and strengtening surveillance. Indian J Pediatr 2002; 69:33-37.
20. Van den Hof S, Conyn-van Spaendonck M, Van Steenbergen JE. Measles epidemic in The Netherlands, 1999–2000. J Infect Dis 2002; 186:1483-1486.
21. Van den Hof S, Smit C, Van Steenbergen JE, et al. Hospitalizations during a measles epidemic in the Netherlands, 1999–2000. Pediatr Infect Dis J 2002; 21:1146-1150.
22. Lertpiriyasuwat C, Kanlayanpotporn J, Deeying J, et al. Measles outbreak in an orphanage, Bangkok, Thailand, September-October 2000. J Med Assoc Thai 2002; 85:653-657.
23. Comittee on Infectious Diseases: Vitamin A treatment of measles. Pediatrics 1993; 91:1014-1015.
24. Griffin DE, Ward BJ, Esolen LM. Pathogenesis of measles virus infection: an hypothesis for altered immune responses. J Infect Dis 1994; 170 (Suppl 1):24-31.
25. Atabani SF, Byrnes AA, Jaye A, et al. Natural measles causes prolonged supression of interleukin–12 production. J Infect Dis 2001; 184:1-9.
26. Mustafa MM, Weitman SD, Winick NJ, et al. Subacute measles encephalitis in the young immunocompromised host: report of two cases diagnosed by polymerase chain reaction and treated with ribavirin and review of the literature. Clin Infect Dis 1993; 16:654-660.
27. Papadopoulu A, Theodoridou M, Syriopoulou V, et al. Hepatitis in children hospitalized with measles: the experience after a Greek epidemic. J Paediatr Child Health 2001; 1:55-57.
28. Okamura A, Itakura O, Yoshiko M, et al. Unusual presentation of measles giant cell pneumonia in a patient with Acquired Immunodeficiency Syndrome. Clin Infect Dis 2001; 32:57-58.
29. Kanra G, Çetin I, Akçören Z, et al. Giant cell pneumonia in a leukemic child in remission: a case report. Turk J Pediatr 2001; 43:338-341.