ONLINE CASE REPORT

Primary Cytomegalovirus-Related Eosinophilic Pneumonia in a Three-year-old Child with Acute Lymphoblastic Leukaemia
Case report and literature review

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الالتهاب الرئوي الإيزينوفيلي الأولي المرتبط بالفيروس المضخم للخلايا في طفل
يبلغ من العمر ثلاث سنوات , ومصاب بسرطان الدم الليمفاوي الحاد
تقرير حالة ومراجعة الأدبيات الطبية

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ABSTRACT: A diagnosis of eosinophilic pneumonia (EP) is rare in patients with acute lymphoblastic leukaemia (ALL). We report a case of EP in association with a primary cytomegalovirus (CMV) infection in a three-year-old Omani child with ALL. The patient presented with fever while undergoing maintenance chemotherapy. He was admitted to the Child Health Department of Royal Hospital, in Muscat, Oman, in November 2011. He was initially thought to have sepsis but failed to respond to antibiotics. Chest computed tomography showed diffuse ground glass lung opacification. Bronchoalveolar lavage (BAL) cytology was consistent with the diagnosis of EP. Polymerase chain reaction tests for CMV were performed on the BAL and blood samples and were both markedly elevated. The patient made a full recovery after treatment with prednisolone and ganciclovir. The association between CMV infection and EP as well as the management of this combination in immunocompromised patients has never been reported in the English literature.

Keywords: Eosinophilic Pneumonia; Cytomegalovirus; Lymphocytic Leukemia; Bronchoalveolar Lavage; Immuno-compromised Patients; Case Report; Oman.

الملخص: يعتبر تشخيص الالتهاب الرئوي الايزينوفيلي نادراً في المرضى المصابين بسرطان الدم الليمفاوي الحاد. نعرض حالة التهاب رئوي إيزينوفيلي مقترن بالتهاب أوّلي للفيروس المضخم للخلايا في طفل يبلغ من العمر ثلاث سنوات ، ومصاب بسرطان الدم الليمفاوي الحاد. أصيب المريض بحمى أثناء العلاج الكيماوي المحافظ. تم تنويم المريض في قسم صحة الطفل بالمستشفى السلطاني بمسقط، عمان في شهر نوفمبر 2011. في البداية كان الاعتقاد أنه مصاب بميكروب في الدم، ولكنه فشل في الاستجابة للمضادات الحيوية. أوضحت الأشعة المقطعية للصدر اصابات على هيئة زجاج باهت في الرئتين. تم اجراء تفاعل البوليميريز المتسلسل للفيروس المضخم للخلايا في عينة الغسل القصبات والأسناخ وعينة للدم ، وكان مرتفعاً بشكل واضح في العينتين. تعافى المريض بشكل كامل بعد علاجه بعقاري البريدنيزولون والجانسيكلوفير. الترابط بين التهاب الفيروس المضخم للخلايا والالتهاب الرئوي الإيزينوفيلي بالإضافة إلى علاج هذا المزيج في المرضى منقوصي المناعة لم يتم تقريره مطلقاً في الأدبيات الطبية الإنكليزية.

مفتاح الكلمات: الالتهاب الرئوي الإيزينوفيلي؛ الفيروس المضخم للخلايا؛ سرطان الدم الليمفاوي الحاد؛ غسل القصبات والأسناخ؛ مرضى منقوصو المناعة؛ تقرير حالة؛ عمان.

EOSINOPHILIC PNEUMONIA IS A RARE condition in the paediatric population.[1,2] It usually presents with acute respiratory distress and eosinophilic pulmonary infiltrates. In most cases, the cause remains idiopathic although patients generally respond well to steroid therapy and do not experience recurrence.[3,4] Cytomegalovirus (CMV) infection has never been reported as a potential cause for this condition nor has it previously been associated with it. This case, to the best of the authors' knowledge, is the first that suggests an association between CMV infection and eosinophilic pneumonia without peripheral eosinophilia.

Case Report

A three-year-old male child in the maintenance phase of chemotherapy for acute lymphoblastic leukaemia (ALL) presented to the Emergency Department of Royal Hospital, in Muscat, Oman, during November 2011. The patient had a low-grade fever which had been present for the previous two weeks. A systemic review revealed no other associated symptoms. He was not known to have suffered from bronchial asthma in the past and had no history of exposure to dust or secondhand smoke. One week prior to presentation he had received a course of chemotherapy consisting

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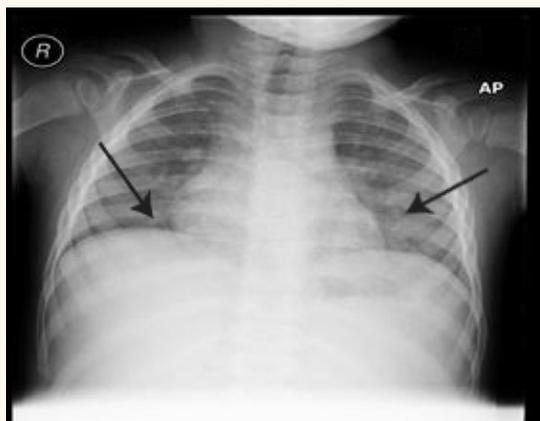*Corresponding Author e-mail: alreesimohammed@gmail.com

Figure 1: Chest X-ray showing poor inspiratory film, with a suspicious bilateral mild diffuse air-space consolidation (black arrows).

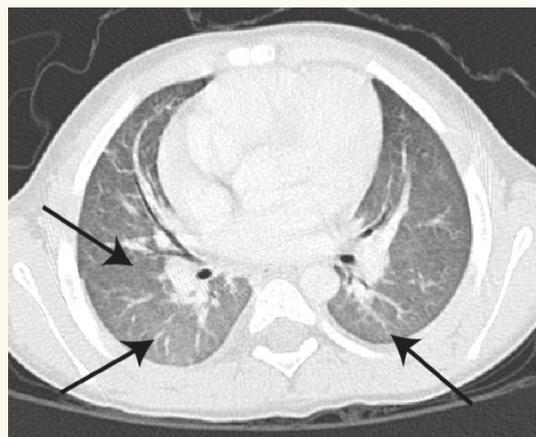*R = right side; AP = anterior-posterior view.*

Figure 2: Axial computed tomography image through the lower lobes of the lungs in the lung window, showing areas of diffuse ground glass appearance in both lungs (arrows).

of intravenous vincristine sulphate and methotrexate. He was then discharged and prescribed oral dexamethasone, mercaptopurine, methotrexate and co-trimoxazole. A physical examination showed that the child was active, haemodynamically stable, with no signs of breathing difficulties and no documented fever. A complete blood count (CBC) showed a haemoglobin (Hb) level of 10.0 g/dL, a platelet count of 233 x 10^9/L, a white blood cell count (WCC) of 1.8 x 10^9/L and an absolute neutrophil count (ANC) of 1.2 x 10^9/L. His C-reactive protein (CRP) was 3.9 mg/L. A peripheral blood culture was taken and the patient was discharged with a prescription for oral amoxicillin and clavulanic acid.

Three days later, the patient's blood culture grew Gram-positive *cocci* and he was requested to return to the hospital. On arrival, he was febrile with a temperature of 38.0 °C, tachypnoeic with a respiratory rate of 40 breaths per minute and tachycardic with a heart rate of 140 beats per minute. His blood pressure was 100/64 mmHg and his oxygen saturation was 100% in room air. The rest of the systemic examination was normal. Investigations showed a slight decrease in Hb level (9.4 g/dL), WCC (1.4 x 10^9/L) and ANC (1.0 x 10^9/L), while a chest radiograph (CXR) was normal. Following blood and urine cultures, the patient was started on piperacillin-tazobactam and vancomycin. Due to his persistent spiking fever, which ranged from 37.8–38.8 °C, he was also prescribed amikacin for superior antimicrobial coverage on the fourth day after admission. On the seventh day post-admission, amphotericin B was administered due to the possibility of a fungal infection.

As the initial blood culture grew Gram-positive *micrococci* of doubtful clinical significance (normal skin *flora*), further investigations were deemed necessary.

A peripheral smear for malaria was negative and bone marrow aspiration did not show any evidence of relapse. Abdominal magnetic resonance imaging did not reveal any deep tissue abscesses or enlarged lymph nodes and a transthoracic echocardiogram ruled out the presence of vegetations.

In addition to the persistent fever, the patient began to develop other clinical signs. His oxygen saturation began to drop and crepitations and wheezing were heard during a chest examination. In addition, hepatomegaly (3 cm below the costal margin) and splenomegaly (2 cm) were identified, both of which had been absent at presentation. A CBC revealed that the ANC had dropped to 0.7 x 10^9/L, while the CRP had increased to 49.5 mg/L. A repeat CXR showed new pulmonary infiltrates [Figure 1]. A computed tomography (CT) scan of the chest and sinuses was subsequently performed to delineate the lung pathology. It showed diffuse ground glass opacification in both lung fields in addition to a few pleural-based nodules possibly representing pleural tags. There were also mild atelectatic changes, mainly in the right middle lobe and *lingula*. No mediastinal lymphadenopathy, pleural effusions, interlobular septal thickening or bronchiectatic changes were noted [Figure 2]. The sinuses were also normal. Although non-specific, these findings were thought to be indicative of an acute process.

In order to determine the specific aetiology of these radiological findings, a bronchoscopy and bronchoalveolar lavage (BAL) were performed. The BAL was negative for pneumocystis *carinii* pneumonia, bacterial and fungal cultures. The cytology of the BAL showed a significant number of eosinophils (>30%), even though there was no peripheral eosinophilia on repeated blood investigations. Based on this finding, a

Table 1: The patient's blood cytomegalovirus polymerase chain reaction results over time

	Copies/mL
Before treatment	160,750
After treatment in days	
1	855,088
6	3128
11	273
18	<10
25	<1*

Below detection level.

diagnosis of eosinophilic pneumonia was made and the patient was started on steroid therapy (2 mg/kg/day of prednisolone). Considering the evidence of hepatosplenomegaly and the fact that the child was immunocompromised, tests for CMV and Epstein-Barr virus were also carried out. Despite having previously been seronegative for CMV, the serology reported positive immunoglobulin M (IgM) and negative immunoglobulin G (IgG) results. The CMV polymerase chain reaction (PCR) in the BAL was positive (1,300 copies/mL), while the blood PCR was highly positive (160,750 copies/mL). A repeat sample of blood for CMV PCR was taken and the patient was started on intravenous ganciclovir (5 mg/kg every 12 hours). After the patient had been on prednisolone for 48 hours, he became afebrile with an improvement in respiratory distress and chest findings. All other antimicrobial agents were discontinued. Prednisolone was tapered off over the following two-week period. His CMV PCR was monitored on a weekly basis and his CBC was monitored twice weekly for cytopoenia. After two weeks of therapy, the CXR was normal and the patient remained afebrile, with a gradual disappearance of his respiratory signs.

During the course of treatment, the patient's chemotherapy was resumed and he required granulocyte colony-stimulating factor (G-CSF) due to neutropaenia. He did not develop thrombocytopoenia and his Hb levels remained within the normal range. His renal function was monitored for nephrotoxicity on a weekly basis but remained within normal limits. The child developed diaphoresis for a few days as a side-effect of ganciclovir; however, this resolved spontaneously. His CMV PCR decreased dramatically over the subsequent weeks [Table 1]. The patient received a full course of parenteral ganciclovir for three weeks, followed by a maintenance phase of oral valganciclovir (15 mg/kg/day) for three weeks. He was discharged after completing the first week of the maintenance phase and was followed up in the outpatient department every two weeks. Throughout

this time he remained asymptomatic. A repeated CMV blood PCR was below detection level and he continued his scheduled chemotherapy course without complications.

Discussion

Paediatric cases of eosinophilic pneumonia are rare, especially in association with ALL.[1,2] Eosinophilic pneumonia is characterised by an acute onset of respiratory distress, radiological evidence of pulmonary infiltrates and significant eosinophilia (>25%) identified through BAL and/or a lung biopsy.[3,5] A physical examination will normally show fever, tachypnoea, bilateral inspiratory crepitations and wheezing.[1,6] The patient described in this case report had an atypical presentation, as the respiratory signs took time to develop and fever was initially the only clinical sign. In an immunocompromised host, the presence of fever has a broad range of differential diagnoses, including infections by different organisms, disease relapse and drug reactions.[7] Therefore, an interventional approach, including any investigations and subsequent management, must be both extensive and aggressive, as they were in the case of the current patient.

The radiological findings in the patient's chest CT scan were consistent with those described in the literature for eosinophilic pneumonia. These can include diffuse areas of ground glass attenuation, alveolar infiltrates, poorly defined nodules and interlobular septal thickening.[8] This diagnosis was confirmed by the BAL cytology findings which determined a significant number of eosinophils (>30%). Similar to previously reported cases, peripheral blood eosinophilia was not present in this patient.[9,10] This may have been because other reported patients were already undergoing oral steroid therapies.[5] Correspondingly, the current patient had been on oral dexamethasone one week before presentation as part of a chemotherapy management plan.

In the majority of cases, eosinophilic pneumonia is idiopathic. However, it can be present in association with different factors, including certain drugs and toxins, smoking, inhaled agents, infections (mainly parasitic), malignant infiltrates and systemic eosinophilic disorders.[11] The current patient did not have a history of exposure to smoke or dust and he was not undergoing a relapse. Among the various drugs he was taking, methotrexate and co-trimoxazole were the only ones which have been reported to cause pulmonary toxicities with eosinophilia.[12,13] However, in addition to the respiratory signs, the patient had

also developed hepatosplenomegaly and experienced a sudden decrease in both his Hb level and ANC. The CMV seroconversion (from the negative IgM and IgG levels recorded two months prior to presentation to positive IgM levels) indicates a primary infection of the virus rather than a reactivation. Although the drop in his CBC parameters may have been primarily related to the chemotherapy, the hepatosplenomegaly, positive CMV serology and significantly high CMV PCR results strongly suggest that CMV infection was the primary aetiology of the eosinophilic pneumonia. It was difficult to establish CMV as the cause of eosinophilic pneumonia in this case due to the fact that a lung biopsy was not performed. However, the positive PCR from the BAL fluid at a time when the patient was also viremic (as evidenced by the positive blood PCR), indicates that it was the likely cause, or at least that there was an association between the CMV infection and eosinophilic pneumonia.

Among the known causes of eosinophilic pneumonia, viruses are considered rare. Nunoda *et al.* reported one case in an adult patient after allogeneic stem cell transplantation for ALL.[14] The PCR for CMV and human herpes virus 6 were positive in both the BAL and blood; these became undetectable after successful treatment with a high dose of methylprednisolone. As a result, Nunoda *et al.* concluded that the eosinophilic pneumonia was an alloreactive response, rather than a condition related to a viral infection.[14] In another reported case, influenza A virus was identified as the cause of eosinophilic pneumonia.[15] Park *et al.* also reported a case of eosinophilic pneumonia in a 14-month-old infant, from which they isolated human bocavirus (HBoV) from nasopharyngeal aspirate by PCR. In this instance, however, they considered the case to be idiopathic as they did not measure the viral load and reported that previous HBoV-related cases of respiratory infections were associated only with mild illness.[1]

It is not uncommon for cases of eosinophilic pneumonia to be misdiagnosed as microbial-related pneumonia or sepsis.[2] This is evidenced by the patient in the current case report, who was empirically treated with antibiotics and antifungal medication before a diagnosis was made. Most patients respond well to steroid therapy and recurrence is not usual.[1,4] In the present case, there was debate among the treating physicians regarding whether steroid treatment alone would be sufficient or whether a specific antiviral agent for CMV infection should be prescribed. It is known that CMV infections in immunocompetent individuals are asymptomatic or cause only mild illness. In immunocompromised patients, however, these infections are associated with high morbiditiy

and mortality.[16] An antiviral agent was therefore preferable for this patient once the diagnosis had been established. Ganciclovir has been shown to be effective in the prevention and treatment of CMV infections in immunocompromised patients, especially if it is given early.[17]

One of the challenges with using this drug, particularly for an immunocompromised host, is the occurrence of cytopoenia as a side-effect. In such cases, G-CSF can be used as a prophylaxis and a treatment for neutropaenia.[18] The neutropaenia in this patient was evident before starting ganciclovir and may have been the result of the CMV infection itself or the previous chemotherapy treatment. Impaired renal function can also develop, especially in patients who are already on other nephrotoxic agents. It is therefore recommended that patients be monitored on a weekly basis during the induction phase of treatment and that PCR is monitored weekly to follow up the patient's response to the antiviral therapy.[19,20]

Conclusion

Eosinophilic pneumonia is a rare disease in children. The aetiology in most cases remains idiopathic. This paper reports a case of eosinophilic pneumonia in association with a CMV primary infection in a child with ALL. Treatment with steroid and antiviral therapy resulted in a complete recovery. The association between eosinophilic pneumonia and CMV infection as well as the management of such a case has never previously been reported in the English literature.

References

1. Park HN, Chung BH, Pyun JE, Lee KC, Choung JT, Lim CH, et al. Idiopathic acute eosinophilic pneumonia in a 14-month-old girl. Korean J Pediatr 2013; 56:37–41. doi: 10.3345/kjp.2013.56.1.37.

2. Oermann CM, Panesar KS, Langston C, Larsen GL, Menendez AA, Schofield DE, et al. Pulmonary infiltrates with eosinophilia syndromes in children. J Pediatr 2000; 136:351–8. doi: 10.1067/mpd.2000.103350.

3. Allen J. Acute eosinophilic pneumonia. Semin Respir Crit Care Med 2006; 27:142–7. doi: 10.1055/s-2006-939517.

4. Sauvaget E, Dellamonica J, Arlaud K, Sanfiorenzo C, Bernardin G, Padovani B, et al. Idiopathic acute eosinophilic pneumonia requiring ECMO in a teenager smoking tobacco and cannabis. Pediatr Pulmonol 2010; 45:1246–9. doi: 10.1002/ppul.21314.

5. Cottin V, Cordier JF. Eosinophilic pneumonias. Allergy 2005; 60:841–57. doi: 10.1111/j.1398-9995.2005.00812.x.

6. Rhee CK, Min KH, Yim NY, Lee JE, Lee NR, Chung MP, et al. Clinical characteristics and corticosteroid treatment of acute eosinophilic pneumonia. Eur Respir J 2013; 41:402–9. doi: 10.1183/09031936.00221811.

7. Peng LH, Keng TC, Sinniah D. Fever in children with acute lymphoblastic leukemia. Cancer 1981; 47:583–7. doi:

10.1002/1097-0142(19810201)47:3<583::AID-CNCR2820470
326>3.0.CO;2-K.

8. Daimon T, Johkoh T, Sumikawa H, Honda O, Fujimoto K, Koga T, et al. Acute eosinophilic pneumonia: Thin-section CT findings in 29 patients. Eur J Radiol 2008; 65:462–7. doi: 10.1016/j.ejrad.2007.04.012.

9. Philit F, Etienne-Mastroïanni B, Parrot A, Guérin C, Robert D, Cordier JF. Idiopathic acute eosinophilic pneumonia: A study of 22 patients. Am J Respir Crit Care Med 2002; 166:1235–9. doi: 10.1164/rccm.2112056.

10. Katz U, Shoenfeld Y. Pulmonary eosinophilia. Clin Rev Allergy Immunol 2008; 34:367–71. doi: 10.1007/s12016-007-8053-y.

11. Pope-Harman AL, Davis WB, Allen ED, Christoforidis AJ, Allen JN. Acute eosinophilic pneumonia: A summary of 15 cases and review of the literature. Medicine (Baltimore) 1996; 75:334–42.

12. Imokawa S, Colby TV, Leslie KO, Helmers RA. Methotrexate pneumonitis: Review of the literature and histopathological findings in nine patients. Eur Respir J 2000; 15:373–81.

13. Marchand E, Cordier JF. Idiopathic chronic eosinophilic pneumonia. Orphanet J Rare Dis 2006; 1:11. doi: 10.1186/1750-1172-1-11.

14. Nunoda K, Sumi M, Takaku T, Tanaka Y, Akahane D, Honda S, et al. [Eosinophilic pneumonia after stem cell transplantation due to alloreactive response in acute lymphoblastic leukemia]. J Tokyo Med Univ 2006; 64:585–9.

15. Jeon EJ, Kim KH, Min KH. Acute eosinophilic pneumonia associated with 2009 influenza A (H1N1). Thorax 2010; 65:268–70. doi: 10.1136/thx.2009.133025.

16. Demmler-Harrison GJ. Cytomegalovirus. In: Feigin RD, Cherry JD, Demmler-Harrison GJ, Kaplan SL. Feigin and Cherry's Textbook of Pediatric Infectious Diseases. 6th ed. Philadelphia, Pennslyvania, USA: Saunders Elsevier, 2009. Pp. 2022–42.

17. Goodrich JM, Boeckh M, Bowden R. Strategies for the prevention of cytomegalovirus disease after marrow transplantation. Clin Infect Dis 1994; 19:287–98. doi: 10.1093/clinids/19.2.287.

18. Drugs for non-HIV viral infections. Treat Guidel Med Lett 2007; 5:59–70.

19. Tice AD, Rehm SJ, Dalovisio JR, Bradley JS, Martinelli LP, Graham DR, et al. Practice guidelines for outpatient parenteral antimicrobial therapy: IDSA guidelines. Clin Infect Dis 2004; 38:1651–72. doi: 10.1086/420939.

20. Weinberg A, Hodges TN, Li S, Cai G, Zamora MR. Comparison of PCR, antigenemia assay, and rapid blood culture for detection and prevention of cytomegalovirus disease after lung transplantation. J Clin Microbiol 2000; 38:768–72.