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Case Report CHILD HEALTH&DISEASES

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Intracranial abscess developed after ganciclovir treatment: A case Report

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ABSTRACT

Neutropenia is defined as the absolute neutrophil count (ANC) falling below 1500/mm^3. The severity of neutropenia is directly related to the ANC. Congenital causes constitute primary, and acquired causes secondary causes of neutropenia. In this report, severe neutropenia secondary to ganciclovir treatment, and associated intracranial abscess in a patient with respiratory insufficiency who required intubation due to CMV pneumonitis.

Keywords: Cranial abscess; cytomegalovirus; ganciclovir; secondary neutropenia.

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Neutropenia is defined as the absolute neutrophil count (ANC) below 1500 cells/mm^3. The severity of neutropenia is associated with absolute neutrophil count (ANC). It is defined as severe neutropenia (ANC <500/mm^3), moderate neutropenia (ANC, <500–1000/mm^3), and mild neutropenia (ANC,<1000–1500/mm^3) [1]. The classification of neutropenia can be done in several different ways, taking into account different characteristics.

Acute neutropenia is defined as a neutropenia lasting shorter than 3 months, and chronic neutropenia lasts longer than 3 months. Congenital causes constitute primary neutropenia, while acquired causes lead to secondary neutropenia [2–4].

Neutropenia is a life-threatening condition that can cause serious infections. Secondary neutropenia is more frequently encountered than primary neutropenia. A number of different etiologies have been shown to cause secondary neutropenia. Some of these are infectious agents, drugs, malnutrition, metabolic diseases, and environmental factors [5, 6]. Drug-related neutropenia is a common condition which can be seen at any age. Drug-related neutropenias may become manifest through many mechanisms.

They can occur with immune mechanisms, but they can be seen following direct suppression of the precursors in the bone marrow. The first approach to treatment is to discontinue neutropenic drugs and to treat with G-CSF [7, 8].

Herein, we would like to present a case of intracranial abscess associated with neutropenia following ganciclovir treatment in a case with normal neutrophil counts.

CASE REPORT

A 6-month-old previously healthy male patient was admitted to the emergency center with cough and respira-

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Table 1. Hemogram, immunglobulins and subgroups of lymphocytes

Hemogram	WBC (mm^3)	Hb (gr/dl)	Plt (mm^3)	ANC (mm^3)	ALC (mm^3)
Immunglobulins					
Subgroups of lymphocytes					
	4500	9.5	445000	470	3360
	9600	10.2	355000	4550	4700
	IgG (mg/dl)	IgM (mg/dl)	IgA (mg/dl)	IgE (mg/dl)	Eosinofil %/(mm^3)
	609	17.3	5.81	18.5	0.9/100
	CD3 (%)/(mm^3)	CD4 (%)/(mm^3)	CD8 (%)/(mm^3)	CD19 (%)/(mm^3)	NK (%)/(mm^3)
	69.7/3275	39.6/1861	25.2/1184	22.8/1071	5/235

tory distress. Posteroanterior chest X-ray demonstrated increased aeration and infiltration in the reticular pattern that established the diagnosis of bronchopneumonia and treatment was initiated. In his follow-up, postero-anterior lung graft suggested progression to respiratory distress syndrome, so acyclovir and oseltamivir was added to the treatment. On the 7th day of the follow-up, his general condition deteriorated and he was taken into the intensive care unit because of the necessity of intubation.

On the respiratory tract pathogenetic agent panel, upon CMV, and CMV PCR positivity, we switched from acyclovir to ganciclovir treatment Four weeks after initiation of ganciclovir therapy CMV PCR negativity was detected, so the treatment was discontinued. The patient experienced seizures, and head control was difficult during the processes of extubation, and weaning from mechanical ventilation while he was followed up in the intensive care unit. Therefore cranial MRI was obtained which revealed a 4.5x3 cm lesion with restricted diffusion consistent with the abscess formation. The patient was operated with the indication of cranial abscess.

Bacterial growth was not detected in cultures of abscess material, and gram staining did not reveal presence of any infectious agent. CMV-PCR test result of the abscess material was reported as negative.

The patient was referred to the Pediatric Immunology Clinic for further investigation of possible underlying immunodeficiency. The first physical examination of the patient did not reveal any pathology regarding skin, cardiovascular and, respiratory systems, and pulmonary vasculature. Lymphadenopathy, hepatosplenomalgy, and microcephaly were not observed and examinations of other systems were unremarkable.

In order to differentiate between congenital and acquired CMV infection of the patient, eye examination, hearing test, cranial MR, and CMV avidity tests were performed. Calcification was not observed on cranial MR in the patient whose ocular examination and hearing test results were within normal limits. The CMV avidity test result was negative. The patient was evaluated in terms of genetics and neurometabolism. In the evaluation of pediatric neurology any the pathology was not detected and the convulsion experienced was interpreted as a manifestation secondary to intracranial abscess. Metabolic tests were reported as normal.

Broad spectrum antibiotherapy (meropenem, vancomycin) was initiated based on blood culture results.

Hemogram of the patient was reported as follows: WBC: 4500/mm^3, neutrophil: 470/mm^3, lymphocyte: 3360/mm^3, Hgb: 9.5 gr/dl, Plt: 445000/mm^3. On peripheral smear atypical cells were not detected, only few neutrophils, and toxic granulation (+) were observed. Immunoglobulins: IgG: 609 mg/dl, IgM: 17.3 mg/dl, IgA: 5.81 mg/dl; Lymphocyte subgroups: CD3: 69.7%; CD4: 39.6%; CD8: 25.2%; CD19: 22.8%; NK: 5.0% (Table 1). The dihydrorodamine test was normal.

Repeated control MRI obtained in our clinic was evaluated in favor of bleeding (Figure 1). The patient was consulted to neurosurgery for operation. During the operation, pus material was drained from the area which was interpreted as hemorrhage and the operation was completed by placing the catheter in the loge. Microbiological examination of the material collected during the operation, and abscess material retrieved from the catheter were unremarkable. Gram staining, and antibiogram could not reveal any bacterial growth in both

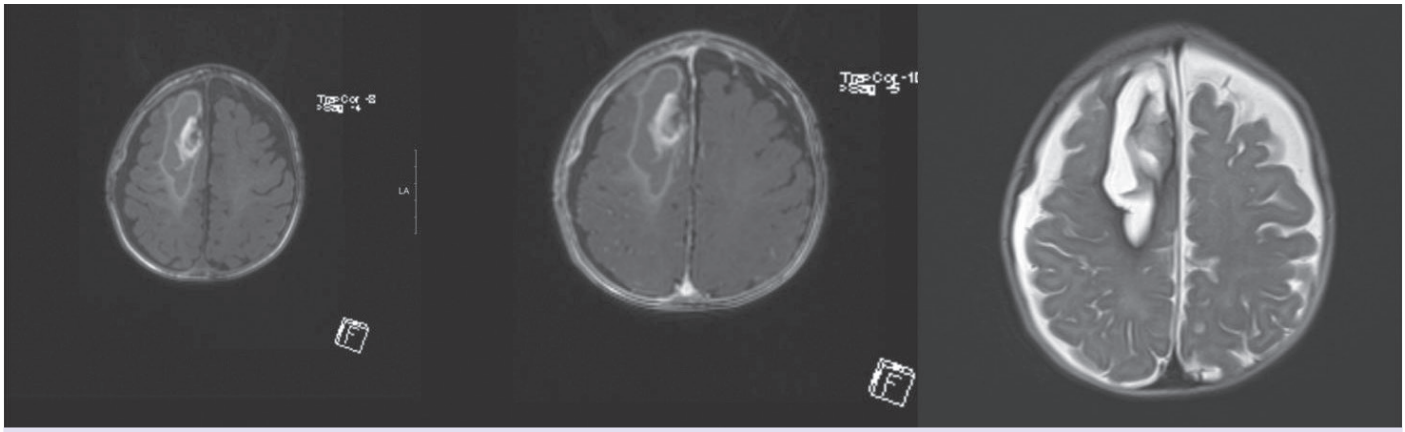

FIGURE 1. Cranial MR T1-weighted contrasted and non-contrasted, T2 –weighted images of the patient.

specimens. Neutropenia was not detected in the evaluation of whole blood counts calculated during healthy periods of the patient, and at the starting time of his first complaints (WBC: 9600/mm^3, Lymphocyte: 4700/mm^3, Neutrophils: 4550/mm^3).

Bone marrow aspiration was performed in order to exclude the primary etiologies, drug-related secondary neutropenia was considered and maturation arrest was not observed. The samples were sent for genetic analysis to exclude possible congenital causes of neutropenia and the result was reported as normal. Cyclic pattern was not observed in the weekly hemogram follow-ups performed to detect cyclic neutropenia.

After exclusion of primary etiologies, since the number of neutrophils calculated during clinical follow-up was within normal limits, infection associated with drug-related secondary neutropenia was considered in the patient who developed neutropenia after CMV infection and ganciclovir treatment. It is thought that cranial abscess developed secondary to these risk factors because of the presence of risk factors such as intubation in the intensive care conditions during this period of neutropenia

Ganciclovir treatment was continued with CMV PCR follow-ups, and when CMV PCR results became negative, neutropenia resolved spontaneously. The patient whose lung infection and cranial abscess treatment completed was discharged with cure. Neutropenia was not detected during clinical follow-up.

DISCUSSION

The etiology of neutropenia in acquired neutropenia involves destruction or consumption of peripheral neutrophils leading to the shortening of neutrophil life. The bone marrow is normal or late maturation in the metamyelocyte / band stage. İs arrested.The risk of developing infections in acquired neutropenia is significantly less than that of other neutropenias [9–11].

Secondary neutropenia can be caused by infections, drugs, autoimmune and isoimmune etiologies [12]. In childhood, the most common etiologies are infections of the secondary neutropenia (viral, bacterial and parasitic). The most common causes of acute secondary neutropenia are viral infections; cytomegalovirus (CMV), Ebstein Barr virus, hepatitis A and B, influenza A and B viruses, measles, parvovirus B19, rubella and chicken pox [13]. Mechanisms of neutropenia secondary to infection involve passage of neutrophils from circulation into marginal pool, sequestration, increased consumption or a decrease in bone marrow reserves [14].

Neutropenia usually begins at the 24th hour of infection and lasts for 3–8 days in those patients who have or had an infection [5]. Infection with CMV leads to neutropenia, through decreased production and increased destruction of neutrophils [12]. Granulocyte-colony-stimulating factor (G-CSF) can be used in neutropenic conditions due to depletion and inadequate production of bone marrow reservoir pools in severe sepsis [10]. Since in our case neutropenia developed at the time of detection of CMV infection and other possible causes have been ruled out, we interpreted the infection in favour of secondary neutropenia.

Drug-related secondary neutropenia may be caused by many drugs. The most frequent causative drug groups include chemotherapy drugs, analgesics and anti-inflammatory agents, antipsychotics, antiepileptics, antithy-

roids, cardiovascular agents, and antibiotics [14].

Mechanisms of neutropenia associated with drugs include idiosyncratic suppression of myeloid production, dose-dependent suppression, suppression due to individual differences in drug metabolisms, and drug-hapten disease -induced destruction [15].

Diagnostic criteria of drug-related neutropenia include neutrophil count below 500 cells/mm^3, hemoglobin level above 10 gr/dl, platelet count above 100,000 cells/mm^3, and drug use history without a causative agent that may cause secondary neuropenia [16, 17]. Ganciclovir idiosyncratically supress myeloid production and causes neutropenia [15].

With the use of medications, neutropenia usually develops within 2–3 months and is expected to resolve within 10 days after discontinuation of the drug. However, sometimes this period can be shorter or longer [12]. In our case, after all other causes were excluded, we thought of secondaryneutropenia due to ganciclovir treatment for infection because of its myelosuppressive effects in the bone marrow In our case, neutropenia resolved within 7–10 days after complete control of the infection and cessation of ganciclovir treatment. and neutropenia did not recur during follow-up period.

Secondary neutropenia due to autoimmune causes is more common in adults and it constitutes a part of autoimmune diseases.

If rheumatologic diseases are not considered in the presence of secondary autoimmune neutropenia in children, firstly autoimmune lymphoproliferative syndrome and Evans syndrome should come to one's mind [18].

Both diseases had findings of lymphadenopathy, splenomegaly, and autoimmunity which were not detected in our patient. Neutropenia is a serious, life-threatening condition and can cause very serious complications. Agranulocytosis increases the susceptibility to many bacterial and fungal infections [19].

Conclusion

Neutropenia is a serious clinical condition with acquired or acquired causes. Clinicians are more likely to encounter secondary neutropenia and it should be kept in mind that life threatening complications such as primary causes may develop in these patients.

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