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Original Article

Eosinophilia and neutropenia in patients with acute rhinopharyngitis in a health center in Peru: an analytical study

Eosinofilia y neutropenia en pacientes con rinofaringitis aguda de un centro de salud de Perú: un estudio analítico

Eosinofilia e neutropenia em pacientes com rinofaringite aguda de um centro de saúde no Peru: um estudo analítico

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ABSTRACT

Introduction. Eosinophils modulate innate and adaptive immunity. Their elevation may be associated with changes in neutrophil concentrations during acute upper respiratory tract infections. The objective was to analyze the association between eosinophilia and neutropenia in patients with acute rhinopharyngitis. **Methodology.** Cross-sectional and analytical study, based on data from medical records of 526 patients from a polyclinic in the district of Villa el Salvador, Peru. Patients diagnosed with acute rhinopharyngitis who underwent a complete blood count were selected. Patients with chronic respiratory and hematologic diseases were excluded. Bivariate statistics with frequencies and percentages were performed, as well as crude and adjusted Odds Ratio tests using binary logistic regression. **Results.** Minors with neutropenia had eosinophilia 5.52 times more often than those without neutropenia (OR=5.52; CI:95%=2.28-13.35; p=0.005). In adults it was 2.01 (OR=2.01; CI:95%=1.07-3.77; p=0.027). **Discussion.** The findings could be attributed to the antiviral activity of eosinophils by

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mechanisms mediated by ribonucleases and neurotoxins, which require neutrophil-mediated activation in the presence of viral and bacterial infectious conditions. In turn, the greater strength of the association in minors could be due to the fact that their immune system is less mature than that of adults, who also take medication more frequently. **Conclusions.** Neutropenia and eosinophilia were more strongly associated in patients with acute rhinopharyngitis, mainly in minors.

Keywords:
Neutrophils; Eosinophils; Common Cold; Adult; Adolescent; Child.

RESUMEN

Introducción. Los eosinófilos modulan la inmunidad innata y adaptativa. Su elevación puede estar asociada a cambios en las concentraciones de neutrófilos durante la infección aguda de vías respiratorias superiores. El objetivo fue analizar la asociación entre eosinofilia y neutropenia en pacientes con rinofaringitis aguda. **Metodología.** Estudio transversal y analítico, basado en datos de historias clínicas de 526 pacientes de un policlínico del distrito de Villa el Salvador, Perú. Fueron seleccionados pacientes diagnosticados por rinofaringitis aguda que se realizaron un hemograma completo. Se excluyó a pacientes con enfermedades respiratorias y hematológicas crónicas. Se realizó estadística bivariada con frecuencias y porcentajes, así como la prueba de *Odds Ratio* crudo y ajustado por regresión logística binaria. **Resultados.** Los menores de edad con neutropenia tuvieron eosinofilia 5.52 veces más a menudo que aquellos sin neutropenia (OR=5.52; IC:95%=2.28-13.35; p=0.005). En adultos fue 2.01 (OR=2.01; IC:95%=1.07-3.77; p=0.027). **Discusión.** Los hallazgos podrían atribuirse a la actividad antiviral de los eosinófilos por mecanismos mediados por ribonucleasas y neurotoxinas, los cuales requieren de la activación mediada por neutrófilos en presencia de cuadros infecciosos virales y bacterianos. A su vez, la mayor fuerza de asociación en menores de edad podría deberse a que su sistema inmunológico está en menor madurez que los adultos, quienes además se medican con mayor frecuencia. **Conclusiones.** La neutropenia y la eosinofilia tuvieron una mayor fuerza de asociación en pacientes con rinofaringitis aguda, principalmente en menores de edad.

Palabras clave:
Neutrófilos; Eosinófilos; Resfriado Común; Adulto; Adolescente; Niño.

RESUMO

Introdução. Os eosinófilos modulam a imunidade inata e adaptativa. Sua elevação pode estar associada a alterações nas concentrações de neutrófilos durante infecção aguda do trato respiratório superior. O objetivo foi analisar a associação entre eosinofilia e neutropenia em pacientes com rinofaringite aguda. **Metodologia.** Estudo transversal e analítico, baseado em dados de prontuários de 526 pacientes de uma policlínica do distrito de Villa el Salvador, Peru. Foram selecionados pacientes com diagnóstico de rinofaringite aguda e submetidos a hemograma completo. Foram excluídos pacientes com doenças respiratórias e hematológicas crônicas. Foram realizadas estatísticas bivariadas com frequências e porcentagens, bem como o teste *Odds Ratio* bruto e ajustado por regressão logística binária. **Resultados.** Menores com neutropenia apresentaram eosinofilia 5.52 vezes mais frequentemente que aqueles sem neutropenia (OR=5.52; IC 95%=2.28-13.35; p=0.005). Nos adultos foi de 2.01 (OR=2.01; IC: 95%=1.07-3.77; p=0.027). **Discussão.** Os achados podem ser atribuídos à atividade antiviral dos eosinófilos através de mecanismos mediados por ribonucleases e neurotoxinas, que requerem ativação mediada por neutrófilos na presença de condições infecciosas virais e bacterianas. Por sua vez, a maior força de associação nos menores pode ser devida ao fato do seu sistema imunitário ser menos maduro do que o dos adultos, que também tomam medicamentos com mais frequência. **Conclusões.** Neutropenia e eosinofilia tiveram maior força de associação nos pacientes com rinofaringite aguda, principalmente nos menores.

Palavras-chave:
Neutrófilos; Eosinófilos; Resfriado Comum; Adulto; Adolescente; Criança.

Introduction

Acute rhinopharyngitis (ARP) is an infection that causes inflammation of the nasal mucosa, presenting a congestive epithelium with deficient immune adaptation in this área (1). The nasopharyngeal cavity is a structure under constant physicochemical and infectious aggression. Under normal conditions, it has an adequate rate of exchange and adaptive congestion based on the functional alternation of the nasal passages; therefore, in ARP, adaptive congestion and deficient immunity combined with infection converge (2).

Causes include viruses, bacteria, and structural factors (polyps, septal deviation, tonsillar hypertrophy) (3). At the onset of infection, neutrophil migration from the medulla to the site of infection occurs, initiating the recognition of pathogen-associated molecular patterns (PAMP), which generates signaling cascades to induce an immune response using multiple pattern recognition

receptors (PRR) on the cell surface, and leads to actions such as phagocytosis, degranulation of myeloperoxidase and lactoferrin, and production of cytokines, chemokines and antimicrobial agents (4). In turn, the inflammation of the infectious condition itself generates migration and activation of eosinophils, causing eosinophilic inflammation of the upper airways, which is mainly related to the appearance and persistence of cough (5).

Neutropenia is the low number of blood neutrophils. Neutrophils constitute 40% to 60% of leukocytes, which act in infections by phagocytosis, degranulation, and extracellular traps (6). Their evaluation is included in the "white blood cell count" test, which measures neutrophils, lymphocytes, monocytes, eosinophils, and basophils (7). Although abnormalities in neutrophil counts are usually caused by intrinsic defects in myelocytes or their precursors, whether neoplasms or inherited genetic diseases, neutropenias secondary to drugs and viral infections are prevalent in the general population, affecting about 5% to 10% of healthy individuals (8).

Eosinophils are leukocytes that mainly participate in the defense against multicellular parasites and allergic processes (9) by releasing granular proteins, reactive oxygen species, enzymes, growth factors, and cytokines, among others (10). They possess ribonucleases that participate in viral infections, such as those produced by the respiratory syncytial virus, influenza, rotavirus, and rhinovirus (11). The increase in eosinophils is called eosinophilia, which can be caused by parasitic infections, allergies, bronchial asthma, as well as by clonal proliferation in hematological disorders and tumors (12).

The role of eosinophils in allergic, parasitic, granulomatous, and fibrotic diseases has been consistently demonstrated (13), but their activity in infections involving neutrophils has been little explored.

There may be some degree of relationship between alterations in neutrophil and eosinophil counts in both adults and children because respiratory infections such as ARP are prevalent nationally and internationally (14) and because neutropenia in infections such as ARP is usually self-limiting and rapidly resolving (15), but with the possibility of recurrence and a high economic cost, representing expenses in the order of millions of dollars worldwide, as well as the loss of work or study days (16), which mainly affects children, adolescents, and older adults or patients with a predisposition to developing recurrent infections. It is also due to the fact that eosinophils can modulate immediate hypersensitivity reactions by degrading or inactivating histamine, which can regulate neutrophil activity (17). Therefore, the aim of this investigation was to evaluate the presence and strength of association between eosinophilia and neutropenia in patients with ARP.

Methodology

his was a cross-sectional and analytical study based on medical records from May 2021 to December 2022 at a polyclinic in the Villa el Salvador district, Lima, Peru. The sampling was non-probabilistic and based on convenience, with a sample of 526 eligible patients divided into two subgroups: one of 132 minors and another of 394 individuals aged 18 years or older.

Our study's inclusion criteria were meticulously designed to ensure the quality of our data. We included patients aged 6 years and older with a clinical diagnosis of ARP, based on symptoms and clinical signs such as rhinorrhea, nasal obstruction, sneezing, pharyngitis, odynophagia, and the observation of pharyngeal erythema during physical examination, with a clinical picture lasting from 7 to 10 days. Additionally, patients had to have undergone a complete blood count. We also implemented a thorough exclusion process, excluding recent or past cases with hematological disorders, neoplasms, bronchial hyperreactivity, or asthma and those with moderate to severe neutropenia (less than 1000 cells per cubic millimeter) or eosinophilia (from 1500 cells per cubic millimeter), as these findings were suggestive of other conditions such as viral diseases, neoplasms, and primary and secondary immunodeficiencies.

The variables used were categorical: age group, neutropenia (yes, no) and eosinophilia (yes, no). The values for neutrophils and eosinophils were determined based on criteria established by the laboratory that processed the samples for the complete blood count using an automated hematological analyzer. Mild neutropenia was considered to be values between 100 and 1500 cells per cubic millimeter, and mild eosinophilia was defined as values between 500 and 1500 cells per cubic millimeter.

A descriptive analysis used absolute and relative frequencies (percentages). The bivariate analysis used the Chi-square test for categorical variables to determine statistical significance. According to the Chi-square goodness-of-fit test, the variables did not have a normal distribution. The Odds Ratio test was performed to assess the strength of the association. The multivariate analysis used binary logistic regression with the following explanatory variables: white blood cell count of eosinophil, monocyte, lymphocyte counts, platelet count, basophils, band neutrophils, segmented neutrophils, and red blood cell count. The cutoff point for statistical significance was set at an alpha value of 0.05.

The Parochial Polyclinic 'Madre de Dios' Ethics Committee approved the research (registration number CMD2021-19). The data were recorded in an anonymous database and coded in Microsoft Excel. Informed consent was not required.

Results

The total number of patients was 526, of which 132 were minors (under 18 years of age), and 394 were 18 or older. Likewise, 74.94% of minors and 39.58% of adults had neutropenia with eosinophilia, respectively (Table 1).

Table 1. Frequency of neutropenia and eosinophilia in patients with ARP

Age-group			Eosinophilia		Total
			Yes	No	
<18 years old	Neutropenia	Yes	30(78.94%)	8(21.06%)	38
		No	38(40.042)	56(59.58%)	94
	Subtotal		**68(51.51)**	**64(48.49)**	**132**
≥18 years old	Neutropenia	Yes	19(39.58%)	29(60.42)	48
		No	85(24.56%)	261(75.43%)	346
	Subtotal		**104(26.39%)**	**290(73.61)**	**394**
Total			172(32.69%)	334(67.31%)	526

Source: prepared by authors.

In minors with ARP, in the 6-11 years age group, it was found that, of 30 children with neutropenia, 24 (80%) had eosinophilia. In the adolescent age group, there was a greater predominance of patients without neutropenia (47.50%) (Table 2).

Table 2. Frequency of neutropenia and eosinophilia in infants and adolescents.

Age-group			Eosinophilia		Total
			Yes	No	
Childhood (6-11 years)	Neutropenia	Yes	24(80%)	6(20%)	30
		No	6(27.27%)	16(72.73%)	22
	Total		**30(57.69%)**	**22(42.31%)**	**52**
Adolescence (12-17 years)	Neutropenia	Yes	6(75%)	2(25%)	8
		No	32(44.44%)	40(55.56%)	72
	Total		**38(47.50%)**	**42(52.50%)**	**80**
Total			68	64	132

Source: prepared by authors.

Minors with neutropenia had eosinophilia 5.52 times more often than minors without neutropenia (OR: 5.52, 95% CI):2.28-13.35; p=0.005). In the age group of 18 years and older with ARP, patients who had neutropenia also had eosinophilia 2.01 times more often than patients without neutropenia (OR=2.01 (CI:95%) =1.07-3.77;p=0.027). In the multivariate analysis, the minor group had an OR of 5.49 (CI: 2.28-13.35; p=0.004), and the adult group had an OR of 2.05 (CI:1.03-3.79;p=0.015) (Table 3).

Table 3. Measures of association between the presence of eosinophilia and neutropenia in patients with ARP adults and underage.

ARP	N	OR	IC:95%	p
<18	132	5.52	2.28-13.35	0.005
≥18 (Adults)	394	2.01	1.07-3.77	0.027
Multivariate Analysis*				
ARP	**N**	**OR**	**IC:95%**	**p**
<18	132	5.49	2.26-13.30	0.004
≥18 (Adults)	394	2.05	1.03-3.79	0.015

*Explanatory variables: white blood cell count of eosinophils, monocytes, lymphocytes, platelet count, basophils, band neutrophils, segmented neutrophils and red blood cell count
p<0.05 CI: Confidence interval, OR: Odds Ratio, ARP: Acute Rhinopharyngitis.
Source: prepared by authors.

Children with neutropenia and ARP had eosinophilia 10 times more often than children without neutropenia (OR:10.66; CI (95%)=1.70-66.72; p=0.007). The result was not statistically significant in adolescents with ARP and eosinophilia (p=0.256; CI:95%= 0.34-38.83) (Table 4).

Table 4. Eosinophilia in children and adolescents with neutropenia

ARP	N	OR	IC:95%	p
Childhood (6-11 years)	52	10.66	1.70-66.72	0.007
Adolescence	80	3.69	0.34-38.83	0.256
Multivariate Analysis*				
ARP	**N**	**OR**	**IC:95%**	**p**
Childhood (6-11 years)	52	10.69	1.73-65.70	0.004
Adolescence	80	3.75	0.39-39.09	0.262

*Explanatory variables: white blood cell count of eosinophils, monocytes, lymphocytes, platelet count, basophils, band neutrophils, segmented neutrophils and red blood cell count.
p<0.05 CI: Confidence interval, OR: Odds Ratio, ARP: Acute Rhinopharyngitis.
Source: prepared by authors.

Discussion

The association between neutropenia and eosinophilia was more robust in patients with ARP, particularly among children under 18, in whom the association was more pronounced than in adults. Neutropenia during respiratory infections (18) is typically transient and asymptomatic, requiring no treatment. Other causes of neutropenia include the use of nonsteroidal anti-inflammatory drugs and antibiotics (19). Eosinophilia is commonly associated with allergic disorders and parasitic infections (20). However, the observed correlation between neutrophils and eosinophils in ARP patients suggests that eosinophils may play a role in antiviral defense and in supporting neutrophil activity. Although the evidence is still preliminary, in vitro studies indicate that neutrophils can activate eosinophils to release enzymes and reactive oxygen species during bronchial inflammation, such as in asthma (21). Moreover, neutrophil activity is regulated by histamine released from mast cells, which is controlled by eosinophils through the enzyme histaminase that degrades histamine via hydrolysis (22). This indicates that the neutropenia and eosinophilia observed in ARP patients may result from increased eosinophil histaminase during nasopharyngeal inflammation.

Few studies have explored the role of eosinophils in viral infections (23). Eosinophil-derived neurotoxin and

ribonuclease may modulate leukocyte chemotaxis (24) and assist in clearing viral RNA (25). Furthermore, eosinophil activity and recruitment have been noted in the bronchi during respiratory viral infections in neonates (26). It has been hypothesized that eosinophils contribute to innate antiviral immunity by promoting the clearance of respiratory viruses through Toll-like receptors (27), which in turn coordinate immune responses against these pathogens. This suggests their involvement in immunity beyond just allergies and parasitic infections. While this study employs a different methodological design, it aligns with previous hypotheses exploring the relationship between neutrophils and eosinophils in inflammatory processes related to viral and bacterial infections. Additionally, the stronger association found in patients under 18 may be attributed to their susceptibility to respiratory infections compared to adults (28), who often rely more on NSAIDs due to a higher prevalence of chronic conditions like hypertension and diabetes.

Some patients did not exhibit neutropenia or developed neutropenia without eosinophilia. The transient nature of these clinical presentations, coupled with the absence of concurrent conditions such as environmental allergens or immune reaction triggers (e.g., asthma or blood pressure medications), may have influenced these cases. Future studies utilizing laboratory samples and biochemical tests could clarify the specific underlying causes.

The study faced limitations related to its methodological design and sample size, which may have introduced bias in the representativeness of the findings for the general population. Potential information bias exists regarding the exclusion criteria, as patients provided some medical histories during interviews. Additionally, observation bias may have occurred due to the lack of laboratory tests to identify specific viruses or bacteria that could have caused the transient symptoms, including C-reactive protein (CRP) levels. This suggests a potential data collection bias related to both participants and measurement methods, as the etiological agents of ARP, including the novel coronavirus (2019), were not explicitly addressed; clinical diagnoses relied on symptomatology, duration, and resolution of signs such as pharyngitis, cough, fever, rhinorrhea, nasal obstruction, and erythema of the pharynx and tonsils, typically lasting 7 to 10 days with a benign course. Another potential information bias could arise from patients not disclosing underlying conditions relevant to the exclusion criteria, although this was managed with verified medical histories. Furthermore, a causal relationship could not be established due to the study's design. The focus was on determining prevalence and the strength of association, and further experimental studies are necessary to explore potential causal relationships between these two immunological and inflammatory processes.

Conclusion

In patients with ARP, neutropenia had a stronger association with eosinophilia than in patients without ARP, mainly in minors. Further experimental studies are needed to identify, quantify, and determine possible direct causal relationships of increased neutrophils and eosinophil counts in patients with ARP, taking into account biological and environmental factors that could influence the interaction between these immunological-inflammatory markers, in order to find an adequate causal relationship, confirming the hypothesis concerning the possible neutrophil-eosinophil interaction in upper respiratory tract infections.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Ethical responsibilities

Protection of people: This study is considered risk-free due to its nature. It was approved by the Institutional Ethics Committee.

Confidentiality of data: The authors declare they have followed their work center's protocols on the publication of patient data.

Right to privacy and informed consent: The authors have obtained the informed consent of patients and/or subjects mentioned in the article. This document is in the possession of the corresponding author referred to in the article

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