



Case Report

# Navigating the Uncommon: A Case of Eosinophilia and Gastroesophageal Symptoms after Ingestion of Nutraceuticals Containing Shiitake Mushroom Compounds

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**Citation:** Varricchi G, Poto R, Lagnese G, Raia M, Scalia G, et al. (2026). Navigating the Uncommon: A Case of Eosinophilia and Gastroesophageal Symptoms after Ingestion of Nutraceuticals Containing Shiitake Mushroom Compounds. Ann Case Report. 11: 2618. DOI: 10.290112574-7754.102618

**Received:** 24 April 2026; **Accepted:** 08 May 2026; **Published:** 19 May 2026

## Abstract

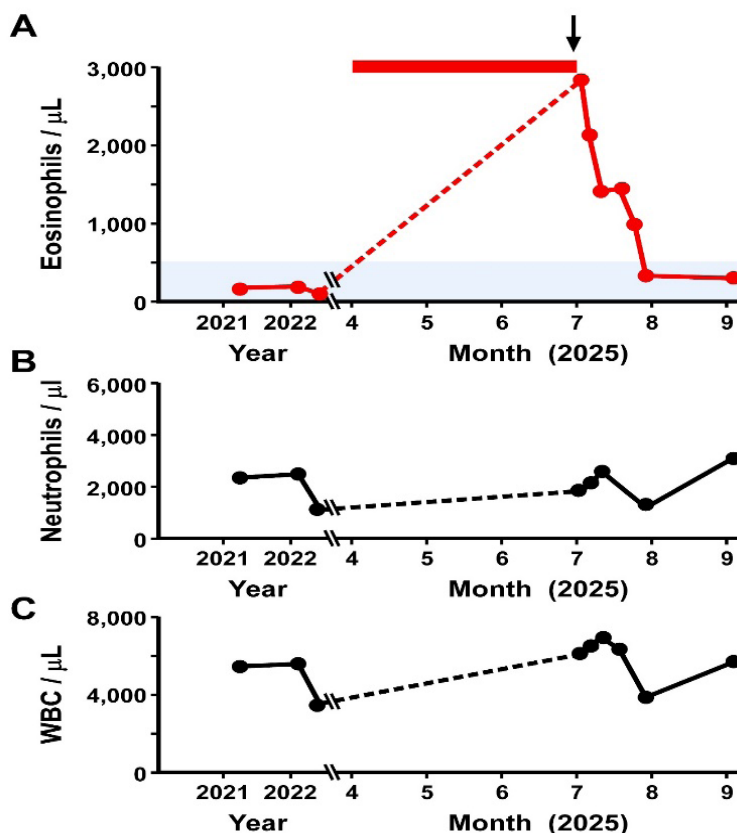
Eosinophils are rare immune cells representing 1%-3% of peripheral blood leukocytes (< 500 cells/ $\mu$ l) in health. These cells have the propensity to leave the blood stream and concentrate at sites of inflammation where can release a plethora of proinflammatory mediators. Eosinophilia is associated with a wide range of diseases with a variety of primary (clonal), secondary, and idiopathic causes. This report presents a case of a 25-year-old woman who developed marked eosinophilia associated with gastroesophageal symptoms after chronic (4 months) intake of a nutraceutical (capsules) containing compounds from Shiitake mushroom. Causes of primary (clonal) causes of hypereosinophilia were excluded, by negative gene rearrangement and flow cytometric analysis. Possible causes of secondary and idiopathic eosinophilia were also excluded. The subject was advised to discontinue use of nutraceutical and was monitored for complete blood count. Eosinophilia and symptoms were progressively reduced with normalization within one month. This case highlights the possibility of eosinophilia in subjects taking nutraceuticals containing Shiitake mushroom compounds and underscores the need for vigilant monitoring of eosinophils during the intake of these preparations.

**Keywords:** Case Report; Eosinophils; Eosinophilia; Gastroesophageal Symptoms: Shiitake Mushroom.

### Case Presentation

A 25-year-old non-smoker woman presented to her doctor with symptoms essentially characterized by epigastralgia. The patient had attributed these symptoms to a period of intense work-related stress. The patient reported having taken, on the advice of a doctor consulted in a different country, a mushroom-derived nutraceutical (capsules) containing Shiitake mushroom compounds (400 mg twice a day) for approximately 4 months. Initial laboratory investigations including full blood count were normal with the exception of marked eosinophilia (40% of peripheral blood corresponding to 2,800 eosinophils/ $\mu$ L). Stool

specimens, examined three times, were negative for parasites. The patient was referred to a specialized Clinical Immunology Center to evaluate all possible primary, secondary, and idiopathic causes of hypereosinophilia. The subject underwent hematological evaluation following the International Consensus Classification Criteria for Hypereosinophilia [1]. Canonical secondary causes (allergies, infections, upper and lower pulmonary and gastrointestinal disorders, immunodeficiencies, autoimmune diseases, and cancer) were carefully excluded. Flow cytometric analysis of peripheral blood excluded eosinophilic leukemia and lymphocyte abnormalities with the exception of marked eosinophilia (Suppl. Figure 1). Primary (clonal) eosinophilia were excluded by negative gene rearrangement (PDGFRA, PDGFRB, FGFR1, JAK2) according to WHO recommendation [1].



**Figure 1:** Kinetics of eosinophils (A), neutrophils (B), and white blood cells (wbc) (C) in peripheral blood before, during and after the intake of capsules containing Shiitake mushroom compounds. The arrow shows the eosinophil levels on the last day of Shiitake intake. The red box shows the period of taking the Shiitake compounds. The blue box shows the range of peripheral blood eosinophils in normal donors.

Shiitake mushrooms (*Lentinula edodes*) are common, edible food widely used in East Asian cuisine. Shiitake mushroom extracts are used in Asian medicine, believed to possess nutraceutical, anti-inflammatory [2, 3], antineoplastic [4, 5], and immunomodulatory properties [6-8]. Dermatitis and eosinophilia have been described in the past and present literature [9-11]. Moreover, a case of eosinophilic esophagitis has been reported after eating Shiitake mushrooms [12]. Based on the laboratory results and the history of taking capsules containing ingredients from Shiitake mushrooms, the patients was advised to discontinue the use of these nutraceuticals. The subject was monitored for symptoms and complete blood count during the following month. Figure 1 shows the patterns of eosinophils, neutrophils, and total leukocytes before the assumption of capsules containing Shiitake mushrooms and after its suspension. Hypereosinophilia was reduced by approximately 50% within two weeks and returned to normal level within one month from stopping taking capsules containing Shiitake mushroom. Flow cytometric analysis of peripheral blood one month from stopping taking Shiitake mushroom containing compounds was normal. Epigastralgia progressively reduced in parallel with the reduction of circulating eosinophils until it disappeared completely.

## Discussion

Eosinophilia is a rare and extremely heterogeneous disorder which can be primary (clonal), secondary, or idiopathic [13-15]. The majority of patients with eosinophilia are associated with a wide spectrum of secondary causes (allergic and autoimmune diseases, drug reactions, vasculitis, infectious diseases, tumors, immunodeficiencies, and graft-versus host disease). Drug-induced diseases represent the main secondary cause of eosinophilia. The case described in this report cannot be strictly considered a drug-induced disorder because capsules containing Shiitake are not considered drugs and are not approved for therapeutic or diagnostic procedure. For this reason too, this case report deserves attention in healthcare field.

Shiitake mushrooms (*Lentinula edodes*) are common, edible food used in East Asian cuisine and medicine, believed to possess nutraceutical, anti-inflammatory [2, 3], antineoplastic [4, 5], and immunomodulatory properties [6-8]. Shiitake mushroom dermatitis and eosinophilia are well documented in the past and present literature [9-11, 16]. Moreover, a case of eosinophilic esophagitis has been reported after eating Shiitake [12]. Interestingly, Levy and collaborators reported that chronic ingestion of Shiitake mushroom powder caused marked eosinophilia and gastrointestinal symptoms in a percentage of normal subjects [17]. Both laboratory and clinical findings resolved within few weeks after the discontinuation of the capsules. The kinetics of both eosinophilia and clinical symptoms described by Levy and collaborators mirror those of our case

supporting the hypothesis that the Shiitake mushroom compounds are responsible for eosinophilia and gastroesophageal symptoms. Shiitake mushrooms contain a myriad of bioactive compounds [18, 19]. These compounds collectively contribute to their hypothetical nutraceutical, anti-inflammatory [2, 3], antineoplastic [4, 5], and immunomodulatory properties [6-8]. The nutraceutic taken in this case contain different bioactive compounds. Therefore, it is not possible to attribute eosinophila to a specific compound.

## Conclusion

This case illustrates the occurrence of moderate hypereosinophilia [20] associated with gastrointestinal symptoms in a subjects assuming a preparation containing Shiitake mushroom. It calls attention to the assumption of these nutraceuticals which are not been evaluated for safety and efficacy by official healthy organization (e.g., FDA, EMA) and can be assumed without medical prescription. It is important also to note that the nutraceutic involved in this case was not intended to cure or prevent any disease. It should be emphasized that eosinophils have the propensity to infiltrate several tissues (e.g., gastrointestinal tract, lung, skin, heart, etc.) causing arm though the release of cationic proteins [i.e., major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil peroxidase (EPX), and eosinophil derived neurotoxin (EDN)] and several proinflammatory mediators [21-23]. Therefore, the chronic administration of nutraceuticals which may cause eosinophilia may determine damage to several organs and symptoms. From a practical point of view, we would like to suggest to monitor a complete blood count during the intake of nutraceuticals potentially associated with eosinophilia.

## Conflict of Interest

We as authors declare that there is no conflict of interest regarding the publication of this article.

## Patient Consent

Written informed consent was obtained from the patient for the publication of their clinical details and any accompanying images. The patient was informed that efforts would be made to conceal their identity and anonymity. A copy of consent form can be provided to the journal upon request to the corresponding author.

## Acknowledgements

The authors thank Dr. Gjada Criscuolo for her excellent managerial assistance in preparing this manuscript. We thank the graphical artist, Fabrizio Forbianco, for preparing Figure 1.

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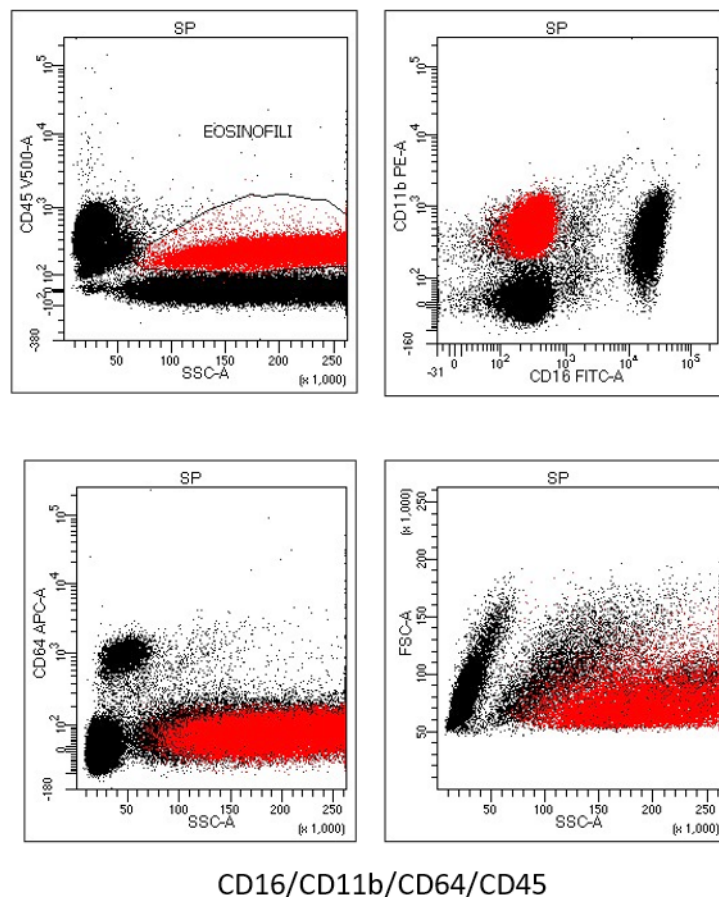
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**Supplementary Fig 1.**



**Suppl. Figure 1.** Flow cytometry. Eosinophil Gating Strategy: Peripheral blood leukocytes were selected based on the expression of CD45, a common pan-leukocyte antigen. Subsequently, the high intensity of CD11b expression, combined with negativity for CD16 and CD64, allows us to discriminate eosinophil granulocytes from neutrophil granulocytes; these are further defined by physical parameters of low FSC and high SSC.