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Seroprevalence of strongyloides stercoralis among cancer patients in an endemic region in Iran

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Abstract

Introduction: Strongyloides stercoralis a globally widespread human intestinal nematode. Hyperinfection mainly appears in patients with defective immune systems . This study intended to investigate the prevalence of serum positive Strongyloides stercoralis in cancer patients who have never undergone chemotherapy and those who received at least one cycle of chemotherapy.

Materials and Methods: This study targeted cancer patients, referred to Rasht hospital, and assigned them to two groups of cancer patients with no history of chemotherapy and cancer patients with at least one cycle of chemotherapy. Patient's demographic information, underlying diseases and chemotherapy regimen were recorded, and their serum sample was examined.

Results: 410 patients were included in this study. the majority were female (51/7%). About 40 patients tested positive for serology, out of which 14 were in the chemotherapy-treated group and 26 in chemotherapy-untreated group, indicating that the prevalence of serum positive Strongyloides stercoralis was significantly higher in patients with no history of chemotherapy. Moreover, eosinophilia significantly correlated with the prevalence of seropositivity. The chemotherapy protocol containing high doses of corticosteroids could multiply the risk of positive serology by 12.7 times.

Conclusion: Before chemotherapy, in areas with a higher prevalence of Strongyloides stercoralis, especially in high corticosteroids protocols, it may make sense to study Strongyloides stercoralis . It becomes more vital in men and eosinophilic patients. Since serologic testing may display false negative rates in patients with defective immune systems, subsequently, alternative complementary methods such as fecal larval examination and fecal PCR test are highly suggested to be carried out along with serology.

Keywords: Strongyloides stercoralis, Serology, Cancer, Chemotherapy

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Introduction

Strongyloides stercoralis is a globally widespread human intestinal nematode that can be easily transmitted esp. in regions with low sanitation conditions. This nematode has an autoinfection cycle in human hosts where it can have a lifelong stay if remained untreated (1-4). Infection of humans with this nematode occurs through the third stage larvae or filariasis that can be through the skin or the mouth feces. The adult female worm lives in the small intestine and is asymptomatic in most people (5, 6). Strongyloides stercoralis mainly appears as gastrointestinal, respiratory (Löffler's syndrome) and peripheral eosinophilic symptoms. Gastrointestinal symptoms of this parasite include nausea, diarrhea and vomiting (7-9). Patients with defective immune systems, AIDS, and malnutrition as well as organ transplant recipients and corticosteroid-treated ones are more prone to the risk of Hyperinfection that will lead to death if left untreated (10-12). An estimated %87 of worldwide deaths are caused by Hyperinfection. Filiform larvae migrate to the heart, liver and central nervous system, resulting in their inflammation and dysfunction in patients with defective immune systems (13, 14). Strongyloides stercoralis is mainly diagnosed through microscopic examination of fecal samples; since this diagnostic method has less sensitivity, many cases remained undiagnosed (15). There are various antigen-based diagnostic methods for testing Strongyloides stercoralis nematode. High sensitivity methods used for diagnosing this nematode involve the use of immunoglobulin isotypes and PCR-based tests for detecting Strongyloides stercoralis-derived DNA in feces (16-18). The sensitivity of ELISA assay technique is about %88-94, having false-negative results in hosts with defective immune systems. Positive rates may appear in the presence of other worm-induced infections. As Strongyloides stercoralis is highly frequent in the northern region of Iran, the present study intended to investigate the prevalence of serum strongyloidiasis in cancer patients who have never undergone chemotherapy and those who received at least one cycle of chemotherapy based on serologic testing because other laboratory testing methods were not available in the intended areas.

Materials and Methods

Study design and study population

This was a descriptive cross-sectional study that was performed on cancer patients admitted on an outpatient basis to Razi Hospital, a referral center in Rasht, north of Iran. The statistical population consisted of two groups of patients: the first group of cancer patients who had not yet received chemotherapy and the second group of patients with cancer who had undergone at least one course of chemotherapy. Patients who have received anti-nematode medication in the past three months, HIV sero-positive, history of organ transplant, or receiving immunosuppression excluded from the study. According to the prior prevalence of Strongyloides stercoralis in chemotherapy-treated (33%) (19) and chemotherapy-untreated (10%) (20) patients, considering 5% confidence limit and 5% margin of error, 236 and 174 sample was determined for chemotherapy-treated and chemotherapy-untreated groups, respectively. This classification was aimed at enabling determination of strongyloidiasis prevalence in patients with and without chemotherapy. The study protocol was approved by the Institutional Review Board of Guilan University of Medical Sciences. Patients were first informed about the purpose of the study and they were taken informed consent to participate in the study.

Data collection

Patient’s demographic information, including age, sex, place of residence, underlying diseases, chemotherapy regimen, current smoking and alcohol consumption were recorded, and their serum sample was collected and examined using serologic tests. ELISA assay was used to detect IgG (Nova Tec Immundiagnostica GmbH, Germany. specificity 94.12%, sensitivity89.47%) . Eosinophilia was defined as an absolute eosinophil count ≥ 500 /microl in peripheral blood.

Statistical analyses

Patients' characteristics and IgG seropositivity were described using frequency and percent. A Chi-square test was applied to detect the association between patients' characteristics and IgG seropositivity. Multivariate logistic regression was used to estimate

adjusted odds ratio (OR) for predictors of seropositivity with 95% confidence interval (CI). A P-value less than 0.05 was considered significant. Data were analyzed using Stata 14.

Results

Out of 410 patients who participated in this study, 212 (%51.7) were female and the highest number of patients (51.5%) were in the age group of 40-60 years. The mean age of participants was 53.27±14.08 years, with the youngest patients aged 17 and oldest 90 years. Table 1 presented demographic information of the patients.

Of the total, 40 patients (%9.8) were positive for IgG serology, out of which 14 (%5.9) were in chemotherapy-treated group and 26 (%14.9) in chemotherapy-untreated group, indicating that the prevalence of serum strongyloidiasis was significantly higher in patients with no history of chemotherapy than chemotherapy-treated ones (P-value: <0.002).

According to the results, there was a significant relationship between sex of patients and the prevalence of serum strongyloidiasis, meaning that serum strongyloidiasis was significantly higher in male than female subjects (P=0.004).

However, other characteristics including place of residence, type of cancer, smoking status, alcohol abuse, underlying diseases, metastasis and chemotherapy sessions, did not significantly correlate with the prevalence of serum strongyloidiasis.

Out of 41 eosinophilic patients, 28 (%68.3) were positive for serology, amongst which 10 (%66.7) were in chemotherapy-treated group and 18 (%69.2) were in chemotherapy-untreated group. Accordingly, there was a significant relationship between eosinophilia and the prevalence of serum strongyloidiasis in cancer patients (P<0.001).

Table 1. prevalence of IgG seropositivity according to the patient's characteristics in Razi medical education center in Rasht.

Variable		Frequency	IgG seropoitivity	
			N	%
Sex	Male	198	28	14.1
	Female	212	12	5.7
Age Range	<40 years	74	5	6.8
	40-60 years	211	18	8.5
	>60 years	125	17	13.6
Occupation	Housewife	123	9	7.3
	Official clerk and Worker	198	20	10.1
	Farmer	41	8	19.5
	Unemployed	48	3	6.2
Place of Residence	City	258	26	10.1
	Village	80	7	8.8
	Urban suburbs	72	7	9.7
Sessions of Chemotherapy*	1-5 sessions	127	5	3.9
	> 5 sessions	109	9	8.3
Eosinophilia	Positive	41	28	68.3
	Negative	369	12	3.3
Corticosteroid-containing regimen*	Yes	22	4	18.2
	No	214	10	4.7
Current Smoking	Yes	106	12	11.3
	No	304	28	9.2
Alcohol consumption	Yes	34	4	11.8
	No	376	36	9.6

* These variables were measured in chemotherapy-treated group

Statistical results showed that 22 of 236 chemotherapy-treated patients had high-dose corticosteroid-containing regimens, 4 of whom (%18.2) tested serologically positive. In other words, there was a significant relationship between the type of chemotherapy regimens and the prevalence of serum strongyloidiasis in patients treated with chemotherapy (P=0.031).

Multivariate logistic regression model status showed that male patients (OR=3.43, 95% CI:1.32-8.89) and eosinophilia (OR=70.6, 95% CI:27.8-178.8) were independent predictors of IgG seropositivity. The sub-group analysis in chemotherapy-treated group revealed that corticosteroid-containing regimen and eosinophilia were independently associated with increased odds of IgG seropositivity.

Discussion

Strongyloidiasis is a parasitic infection with widespread distribution in regions with a humid climate like the north of Iran. It is associated with the risk of death in people with an immunosuppressive system .

According to the results of this study, serum positive Strongyloides stercoralis was more prevalent in cancer patients by 9.8 percent (5.9-14.9). Baiomy et al. (2010) found an approximated %6.3 frequency of serum strongyloidiasis in Egypt (21). As reported by Rafiei et al. (2016), Ahvaz showed %14.4 prevalence of the disease (20). In preceding Iranian studies, strongyloidiasis was more widespread in northern regions of Iran such as Guilan due to their humid climate. Sajjadi et al. (2002) showed that the prevalence of strongyloidiasis was %6.1 (22). As this study indicated, the risk of positive serology was significantly higher in chemotherapy-untreated than chemotherapy-treated patients; the reason may contribute to the false negative results of serologic tests, generation of various antibody subtypes and failure to find antibodies in acute phase of the disease. The presence of other parasites such as schistosomiasis, ascaris, etc. may associate with positive serology. Mendez et al. (2016) revealed that false negative serologic test results were allied to a defective immune system, with higher rates in chemotherapy-treated than chemotherapy-untreated patients. Other causes of false negatives depend on the emergence of various antibody subtypes, except for IgG, as well as the lack of antibodies in acute phase of the disease (23). In a fecal examination, Azizi et al. (2012) showed that intestinal parasites were prevalent in the group of chemotherapy-treated patients by %24.8 and in chemotherapy-untreated group by %28 (24). Similarly, the observed frequency was higher in patients untreated with chemotherapy than those treated with chemotherapy in this study; that is because of the effect of chemotherapy drugs on parasite growth control and exposure for patients in critical care unit .

Eosinophilia increased the risk of positive serology by 70, which was in line with Ashrafi's et al. (2008) study in Guilan (25). Lotfi et al. (2002) reported eosinophilia in about %83 of patients with strongyloidiasis (26).

According to Mendez et al. (2016), eosinophilia was more frequently witnessed in patients with strongyloidiasis (23).

Corticosteroids can suppress the immune system at certain doses and provide the ground for the risk of different parasitic and bacterial infections. The results of this study were representative of statistical relationship between corticosteroid-containing chemotherapy regimen and the prevalence of serum strongyloidiasis, implying that corticosteroid can increase the risk of positive strongyloidiasis serology by 12.7 times in chemotherapy-treated patients. Fardet et al. (2007) stated that strongyloidiasis should be considered a potential risk in all corticosteroid recipients (27). Corti et al. (2016) found that strongyloidiasis appeared as Hyperinfection in immunosuppressive patients esp. recipients of high-dose corticosteroid in Argentina (28). According to Keiser's et al. (2004) study in Maryland, immunosuppression is associated with Hyperinfection in strongyloidiasis with the significant effect of corticosteroid (29). Mendez et al. (2016) found that corticosteroid is the most common risk factor for strongyloidiasis progress even in its short-term use (23).

Furthermore, the findings of this study displayed that male patients were 3.6 times more prone to the risk of positive serology. In their study, Sharif Dini et al. (2018) showed that infection was more prevalent in

men due to their frequent exposure to infectious sources in outdoor activities and open-air jobs (30). Another main category in cancer investigations besides genetics and also clinical investigations is the fluctuation of DNA methylation. Meaningly, DNA methylation is one of the most important parts of epigenetics that always has a notable impression on carcinogenesis and tumorigenesis. Consequently, it is recommended that selecting some important genes and also the investigating of their epigenetics (DNA methylation) can lead to a notable result (31-35).

In finale, there was no significant relationship between the prevalence of serum positive strongyloidiasis and patients' age, occupation, type of cancer, metastasis, chemotherapy sessions, smoking status, alcohol abuse and place of residence in this study.

Conclusions

Regarding the risk of exacerbation of the disease and the spread of widespread disease in immunocompromised individuals, it is recommended that people with cancer who are scheduled to receive a corticosteroid regimen be screened for chemotherapy before chemotherapy to prevent the disease from progressing. It is more important in men with eosinophilia. Since the prevalence of strongyloidiasis appeared to be lower in chemotherapy-treated patients than chemotherapy-untreated ones, serologic testing method per se seems to be not sufficient; subsequently, further studies with larger sample size and fecal PCR-DNA comparisons are suggested to be carried out along with serology testing. Moreover, as testing results may display false negative rates in chemotherapy-treated patients, endemic regions should be serologically tested for the disease before initiating chemotherapy.

Author contribution

FN is hematologist and medical oncologist managed the patients and participated in the drafted manuscript. **ASh** is gasterentrologist managed the patients and participated in the drafted manuscript. **MSh** performed statistical analysis. **SGh** collected data and manage the patients. **ShD** collected data and participated in the drafted manuscript. All the authors read and approved the final manuscript**.**

Ethical approval

This study was approved by the ethic committee of guilan university of medical sciences with ethics code of IR.GUMS.REC.1398.110.

Conflict of interest

No potential conflict of interest was reported by the authors.

References

1. Mejia R, Nutman TB. Screening, prevention, and treatment for hyperinfection syndrome and disseminated infections caused by Strongyloides stercoralis. Curr Opin Infect Dis. 2012;25(4):458-63.

2. Nutman TB. Human infection with Strongyloides stercoralis and other related Strongyloides species. Parasitology. 2017;144(3):263-273.

3. Henriquez-Camacho C, Gotuzzo E, Echevarria J, White AC Jr, Terashima A, Samalvides F, Pérez-Molina JA, Plana MN. Ivermectin versus albendazole or thiabendazole for Strongyloides stercoralis infection. Cochrane Database Syst Rev. 2016;18;2016(1):CD007745.

4. Jourdan PM, Lamberton PHL, Fenwick A, Addiss DG. Strongyloides stercoralis: the need for accurate information - Authors' reply. Lancet. 2018;9;391(10137):2323.

5. Greaves D, Coggle S, Pollard C, Aliyu SH, Moore EM. Strongyloides stercoralis infection. BMJ. 2013;30;347:f4610.

6. Patil RK, Ghosh KK, Chandrakala S, Shetty S. A possible need for routine screening for Strongyloides stercoralis infection in Indian haemophilia patients. Indian J Med Res. 2018;147(3):315-317.

7. Higashiarakawa M, Hirata T, Tanaka T, Parrott G, Kinjo T, Naka H, Hokama A, Fujita J. Normal serum IgE levels and eosinophil counts exhibited during Strongyloides stercoralis infection. Parasitol Int. 2017;66(1):807-812.

8. Rewerska J, Guzman G. 244 Inclusion of Strongyloides stercoralis Infection in the Differential Diagnoses of Nonspecific Gastrointestinal Symptoms and Hypereosinophilia Among Immunocompromised

Patients With a History of Outside Travel. Am J Clin Pathol. 2018;149(suppl_1):S104-S.

9. Tamarozzi F, Martello E, Giorli G, Fittipaldo A, Staffolani S, Montresor A, Bisoffi Z, Buonfrate D. Morbidity Associated with Chronic Strongyloides stercoralis Infection: A Systematic Review and Meta-Analysis. Am J Trop Med Hyg. 2019;100(6):1305-1311.

10. Patton JB, Bonne-Année S, Deckman J, Hess JA, Torigian A, Nolan TJ, Wang Z, Kliewer SA, Durham AC, Lee JJ, Eberhard ML, Mangelsdorf DJ, Lok JB, Abraham D. Methylprednisolone acetate induces, and Δ7-dafachronic acid suppresses, Strongyloides stercoralis hyperinfection in NSG mice. Proc Natl Acad Sci U S A. 2018;2;115(1):204-209.

11. Rao S, Tsai H, Tsai E, Nakanishi Y, Bulat R. Strongyloides stercoralis Hyperinfection Syndrome as a Cause of Fatal Gastrointestinal Hemorrhage. ACG Case Rep J. 2019;15;6(3):1-3.

12. Pan D, Arkell P, Stone NRH, Parkinson B, Tinwell B, Cosgrove CA. Delayed Strongyloides stercoralis hyperinfection syndrome in a renal transplant patient with Pneumocystis jirovecii pneumonia receiving high-dose corticosteroids. Lancet. 2019 Apr 13;393(10180):1536.

13. Thaden J, Cassar A, Vaa B, Phillips S, Burkhart H, Aubry M, Nishimura R. Eosinophilic endocarditis and Strongyloides stercoralis. Am J Cardiol. 2013;1;112(3):461-2.

14. Concha R, Harrington W Jr, Rogers AI. Intestinal strongyloidiasis: recognition, management, and determinants of outcome. J Clin Gastroenterol. 2005;39(3):203-11.

15. Yunus MH, Arifin N, Balachandra D, Anuar NS, Noordin R. Lateral Flow Dipstick Test for Serodiagnosis of Strongyloidiasis. Am J Trop Med Hyg. 2019;101(2):432-435.

16. Schär F, Odermatt P, Khieu V, Panning M, Duong S, Muth S, Marti H, Kramme S. Evaluation of real-time PCR for Strongyloides stercoralis and hookworm as diagnostic tool in asymptomatic schoolchildren in Cambodia. Acta Trop. 2013;126(2):89-92.

17. Arifin N, Hanafiah KM, Ahmad H, Noordin R. Serodiagnosis and early detection of Strongyloides stercoralis infection. J Microbiol Immunol Infect. 2019;52(3):371-378.

18. Sears WJ, Nutman TB. Strongy Detect: Preliminary Validation of a Prototype Recombinant Ss-NIE/Ss-IR Based ELISA to Detect Strongyloides stercoralis Infection. PLoS Negl Trop Dis. 2022;25;16(1):e0010126.

19. Zueter AM, Mohamed Z, Abdullah AD, Mohamad N, Arifin N, Othman N, Noordin R. Detection of Strongyloides stercoralis infection among cancer patients in a major hospital in Kelantan, Malaysia. Singapore Med J. 2014;55(7):367-71.

20. Rafiei R, Rafiei A, Rahdar M, Keikhaie B. Seroepidemiology of Strongyloides stercoralis amongst immunocompromised patients in Southwest Iran. Parasite Epidemiol Control. 2016 ;5;1(3):229-232.

21. Baiomy AM, Mohamed KA, Ghannam MA, Shahat SA, Al-Saadawy AS. Opportunistic parasitic infections among immunocompromised Egyptian patients. J Egypt Soc Parasitol. 2010;40(3):797-808.

22. F A. Medical helminthology Tehran: Keshavarz. 2002.

23. Requena-Méndez A, Buonfrate D, Gomez-Junyent J, Zammarchi L, Bisoffi Z, Muñoz J. Evidence-Based Guidelines for Screening and Management of Strongyloidiasis in Non-Endemic Countries. Am J Trop Med Hyg. 2017;97(3):645-652.

24. Azizi, M., Houshyar, H., Mousavi, G.A., Arbabi, M. and Zahiri, A. "Investigation the relationship between chemotherapy and intestinal parasitic infections in cancer patients undergoing chemotherapy. 2012; 42-48.

25. Ashrafi K, Tahbaz A, Rahmati B. Strongyloides stercoralis: The Most Prevalent Parasitic Cause of Eosinophilia in Gilan Province, Northern Iran. Iran J Parasitol. 2010;5(3):40-7.

26. Loutfy MR, Wilson M, Keystone JS, Kain KC. Serology and eosinophil count in the diagnosis and management of strongyloidiasis in a non-endemic area. Am J Trop Med Hyg. 2002;66(6):749-52.

27. Fardet L, Généreau T, Poirot JL, Guidet B, Kettaneh A, Cabane J. Severe strongyloidiasis in corticosteroid-treated patients: case series and literature review. J Infect. 2007;54(1):18-27.

28. Corti M. Strongyloides stercoralis in immunosuppressed patients. Arch Clin Infect Dis. 2016 1;11(1).

29. Keiser PB, Nutman TB. Strongyloides stercoralis in the Immunocompromised Population. Clin Microbiol Rev. 2004;17(1):208-17.

30. Sharifdini M, Keyhani A, Eshraghian MR, Beigom Kia E. Molecular diagnosis of strongyloidiasis in a population of an endemic area through nested-PCR. Gastroenterol Hepatol Bed Bench. 2018;11(1):68-74.

31. Ghadami E, Nikbakhsh N, Fattahi S, Kosari-Monfared M, Ranaee M, Taheri H, Amjadi-Moheb F, Godazandeh G, Shafaei S, Nosrati A, Pilehchian Langroudi M, Samadani AA, Amirbozorgi G, Mirnia V, Akhavan-Niaki H. Epigenetic alterations of CYLD promoter modulate its expression in gastric adenocarcinoma: A footprint of infections. J Cell Physiol. 2019;234(4):4115-4124.

32. Pilehchian Langroudi M, Nikbakhsh N, Samadani AA, Fattahi S, Taheri H, Shafaei S, Amirbozorgi G, Pilehchian Langroudi R, Akhavan-Niaki H. FAT4 hypermethylation and grade dependent downregulation in gastric adenocarcinoma. J Cell Commun Signal. 2017;11(1):69-75.

33. Samadani AA, Nikbakhsh N, Pilehchian M, Fattahi S, Akhavan-Niaki H. Epigenetic changes of CDX2 in gastric adenocarcinoma. J Cell Commun Signal. 2016;10(4):267-272.

34. Samadani AA, Noroollahi SE, Mansour-Ghanaei F, Rashidy-Pour A, Joukar F, Bandegi AR. Fluctuations of epigenetic regulations in human gastric Adenocarcinoma: How does it affect? Biomed Pharmacother. 2019;109:144-156.

35. Kosari-Monfared M, Nikbakhsh N, Fattahi S, Ghadami E, Ranaei M, Taheri H, Amjadi-Moheb F, Godazandeh GA, Shafaei S, Pilehchian-Langroudi M, Samadani AA, Akhavan-Niaki H. CTNNBIP1 downregulation is associated with tumor grade and viral infections in gastric adenocarcinoma. J Cell Physiol. 2019;234(3):2895-2904.