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A case report of *Blastocystis* infection and Steven Johnson's syndrome

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Abstract. *Blastocystis* species (spp.) is an emerging pathogen. There are several unsolved issues linked to this parasite ranging from its nomenclature, commensal status, standardization of laboratory diagnostic methods, genotypes and treatment. Recently, there has been an increase in reports of *Blastocystis* spp. from symptomatic cases which provide enough evidence of its pathogenic potential. A range of signs and symptoms, from gastro-intestinal to cutaneous manifestations have been attributed to *Blastocystis* infection. Few reports have established an association between intestinal infection with *Blastocystis* spp. and skin manifestations in form of urticaria, palmoplantar pruritus and allergy with complete resolution of cutaneous lesions with eradication of the parasite. In this report, we describe a case of Steven Johnson's syndrome (SJS) in a 6 years old girl along with infection with *Blastocystis* spp. marked by diarrhea and abdominal pain. Stool examination revealed the presence of all forms of the parasite with subsequent decrease in parasite burden and diarrhea over a period of time. Interestingly, the clearance of *Blastocystis* spp. from stool was followed by recovery from skin lesions and other symptoms. In this case, the course of SJS was clearly associated with *Blastocystis* infection. Though skin manifestation with *Blastocystis* infection has been previously reported, this is the first report of its association with SJS. This report indicates newer insights of the parasite that are less well studied.

INTRODUCTION

Blastocystis species (spp.) is the most commonly found parasite in the stool samples in the underdeveloped and developing countries (Tan, 2008). The global prevalence of *Blastocystis* ranges from 0.5% to 62% worldwide (Clark *et al.*, 2013). The prevalence of *Blastocystis* is 1.5-10% in developed countries as against 30-50% in the developing countries (Chen *et al.*, 2003). Children in countries with low socio-economic status have a higher incidence of this infection which can be attributed to poor hygiene and consumption of contaminated food and water (Coyle *et al.*, 2011). A study from West Africa reported 100% prevalence of *Blastocystis* among the school children (El Safadi *et al.*, 2014). In India, the occurrence of *Blastocystis* in stool is 15% among the healthy individuals, and the incidence rises to 33.34% in patients with irritable bowel syndrome (Das *et al.*, 2016). Formerly known as *Blastocystis hominis* when isolated from clinical samples, its huge genetic diversity has now restricted its name to *Blastocystis* spp. only. Besides its pathogenic role in immunocompromised hosts, various associations with cancer, arthritis, irritable bowel syndrome have been previously studied (Noureldin *et al.*, 1999; Tasova *et al.*, 2000; Kurniawan *et al.*, 2009; Mirza & Tan, 2012). The rapid proliferation of *Blastocystis* in the gut leads to severe diarrhea (Carbajal *et al.*, 1997) but its self-limiting nature works as an obstruction for

identification of this parasite as a prominent cause. Interestingly, *Blastocystis* infection has also been associated with several skin manifestations like acute and chronic urticarial, allergy (Valsecchi *et al.*, 2004; Zaglool *et al.*, 2012; Salvador *et al.*, 2016), palmoplantar pruritus (Kick *et al.*, 2002) and alleviation of skin lesions have been reported with the eradication of *Blastocystis* spp.

Steven Johnson's syndrome (SJS) is a rare disorder of the skin and mucous membrane following a reaction to medication or infection. The actual cause of SJS remains unidentified in about one-quater to one half of the cases. However in past, protozoan parasites have also been considered as possible causes of the disease (Foster *et al.*, 2013). In this report, we present a case of acute diarrhea due to *Blastocystis* infection in a patient with SJS. Though the actual cause of SJS could not be elucidated in this case, the course of the disease well corroborated with *Blastocystis* infection. As several other skin conditions has been reported previously with *Blastocystis* infection along with their disappearance with eradication of the parasite, it was logical to think that in absence of other causes, SJS can also be associated with *Blastocystis* infection as in this report. This case emphasizes the importance of routine stool examination for parasites in patients with SJS who are non-responsive to primary treatment.

CASE REPORT

A six years old girl from outskirts of Varanasi, India presented to the Dermatology outpatient department of the tertiary care hospital of Institute of Medical Sciences, Banaras Hindu University, Varanasi, India with burn like lesions all over the face and upper part of the chest along with high fever. She also complained of lower abdominal pain about a week before the onset of the lesions. Her past history revealed intake of some unknown medications from a local practitioner for fever following which there was appearance of the lesions. A provisional diagnosis of SJS was made probably due to some non-steroidal anti-inflammatory drugs (NSAIDS) or antibiotics and she was admitted in the hospital for management. On physical examination she was febrile with a body temperature of 102.2°F and pulse rate of 133 per minute. She had difficulty in swallowing and was kept on high protein diet. She occasionally complained of vague abdominal pain but showed no tenderness on examination. Her blood culture report was negative for bacterial and fungal growth and viral serological profile for herpesviruses, dengue, chikungunya and malaria was also negative. She was kept on clindamycin (100 mg twice daily), piperacillin-tazobactum (2g thrice daily, intravenous) linezolid (200mg twice daily), fluconazole (100mg once weekly) and pantoprazole (20mg once daily) in order to treat any undiagnosed blood stream infection responsible for high grade fever. Topical fusidic acid and clotrimazole mouth paint was applied for the cutaneous and oral lesions every 6 hours. She was haemodynamically stable and other investigations like complete blood count, liver function and renal functions tests were within normal limits. The patient however did not respond to medication and over a course of a week's time complained of consistent abdominal pain and passage of loose stool along with fever. On light microscopic examination of stool, presence of numerous granular and vacuolar forms of *Blastocystis* spp. (>5 cysts/HPF) was revealed along with occasional amoeboid and cyst forms (Fig. 1A, B). As the child was already sensitive to certain unknown medications, monitoring of parasite load in stool samples for 3 successive days was decided prior to initiation of metronidazole therapy. Subsequent stool samples revealed decrease in parasite burden with reduced excretion of vacuolar and granular forms (< 3 cyst/HPF) along with complete absence of amoeboid and cyst form from the 3rd day since onset of diarrhea. The self-limiting nature of the infection was confirmed by gradual decrease in parasite excretion in successive stool samples. Surprisingly, along with alleviation of diarrhea, there was subsiding of skin lesions, fever and abdominal pain and complete absence of *Blastocystis* spp. in

stool within 7 days of the acute episode. The patient recovered well and was discharged after 15 days of hospital stay. The patient was followed up for three months but was negative for the presence of *Blastocystis* spp. in stool. Though it was not conclusive whether SJS was mediated by *Blastocystis* infection in this child, the presence and absence of parasites in stool well correlated with the clinical manifestations of the condition. Informed consent was obtained from the guardian of the patient for presentation of the case report.

IDENTIFICATION

Direct wet mount preparations of the stool sample revealed the presence of numerous granular and vacuolar forms and also amoeboid and cyst forms. Further, study of the detailed structure of the forms of the parasite was performed by trichome staining which confirmed their presence (Fig. 1). The amoeboid form, which marks the pathogenic strains, were non-motile and without prominent pseudopodia as shown in Fig. 1A. This form was expected as the patient was symptomatic. The common forms like vacuolar and granular form has been shown in Fig. 1 A,C,D. Vacuolar forms were seen to contain large central bodies with their peripheral cytoplasm (Fig. 1D). As state of the art diagnosis for *Blastocystis* is detection by polymerase chain reaction (PCR), the identification of the parasite was further ascertained by molecular detection based on previous reference (Yoshikawa *et al.*, 2000). Fig. 2 shows the presence of the *Blastocystis* in stool detected by SSU r DNA PCR.

DISCUSSION

Blastocystis spp. is a parasitic protozoan frequently found in the intestinal tract of humans. Although there are not enough reports to support the pathogenicity of *Blastocystis* spp., but the epidemiological data suggest strong pathogenic potential of

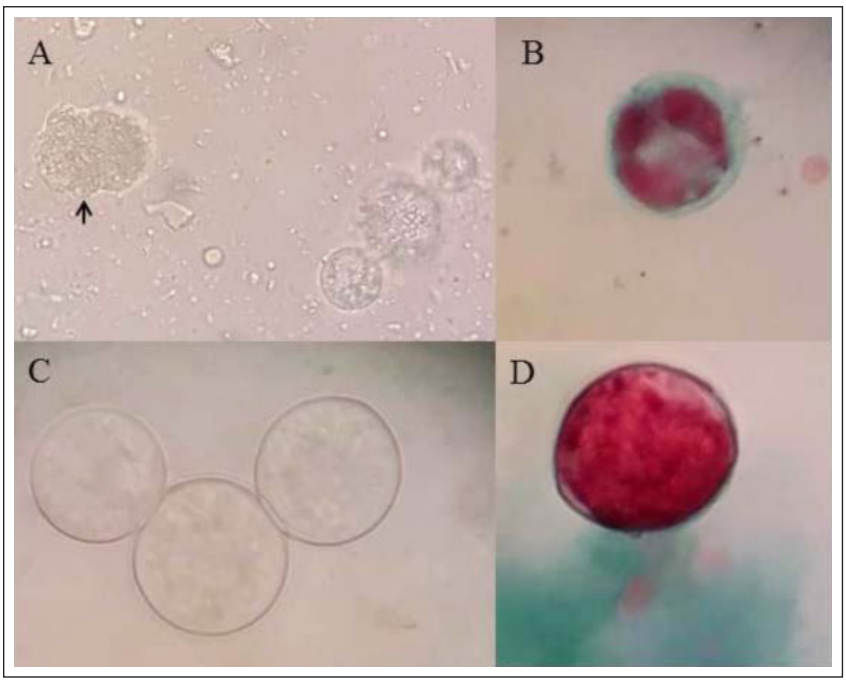

Figure 1. Wet mount and trichrome stained smears of *Blastocystis* spp. in stool. A: Wet mount (40X) showing amoebic (arrow) and granular forms; B: Trichrome stained smear (100X) showing cyst forms; C: Wet mount smear showing vacuolar forms; D: Trichrome stained smear showing vacuolar form.

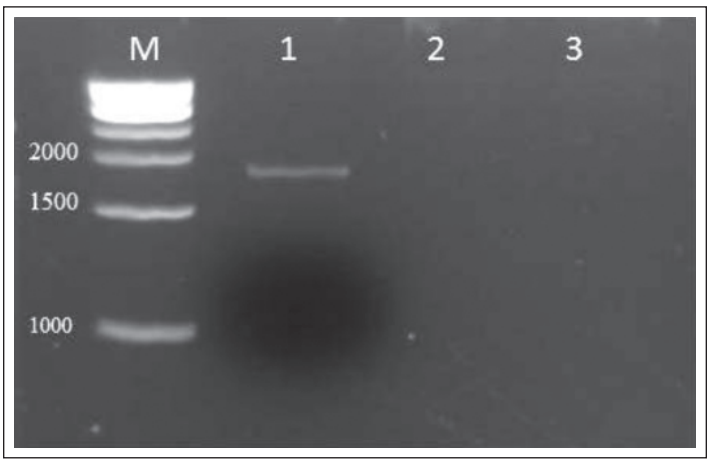

Figure 2. Amplification of SSU rDNA for detection of *Blastocystis* spp. in stool.
Lane M: 1Kb DNA ladder (NE Biolabs); Lane 1: Presence of *Blastocystis* spp. in stool (SSU rDNA, 1780bp); Lanes 2-3: Subsequent stool samples negative for *Blastocystis* spp.

this parasite (Tan & Suresh, 2006). Most of the *Blastocystis* infections are self-limiting, as seen in this case which makes its recognition difficult. The parasite is polymorphic in existence with vacuolar and granular forms as the predominant ones seen in clinical samples. The other forms namely amoebic and more recently described cystic forms are rarely reported (Tan & Suresh, 2006). However, in the present case all forms of the parasite was simultaneously seen in stool sample which could have been responsible for the symptoms in this patient.

SJS is a very rare immune system mediated hypersensitivity reaction. It becomes more severe when combined with the toxic epidermal necrolysis (TEN). The incidence of SJS is 1 to 6 per million people and for TEN its 0.4 to 1.2 per million people each year (Yang *et al*., 2016). SJS is either medications induced or infection induced (Tan & Suresh, 2006), however genetically induced cases have also been reported (Foster *et al*., 2013). The infectious agent for SJS can be of bacterial origin, viral or fungal origin. Nevertheless, association of a few protozoan infections, like malaria and trichomoniasis, with SJS has been reported earlier (Tan & Suresh, 2006). This case report focuses on the association between the parasitic protozoan *Blastocystis* spp. and SJS. The otherwise non-responsive skin lesions subsided with control of the self-limiting *Blastocystis* infection. This clearly hints towards an association between presence of the parasite and the diseased condition.

Little is known about the occurrence of cutaneous symptoms as a manifestation of *Blastocystis* infection. However a previous report had suggested association of chronic spontaneous urticaria with intestinal parasites among which *Blastocystis* spp. is the most frequent and relevant parasite (Kolkhir *et al*., 2016). This report for the first time indicates probable association of SJS with this parasite. Besides, one study on cutaneous manifestation of infection with this parasite had suggested routine stool examination for this parasite in all patients with idiopathic skin lesions (Balint *et al.*, 2014). While urticaria could be due to IgE mediated tissue inflammation against self-antigens of *Blastocystis* spp. (Kolkhir *et al*., 2016) similar mechanisms could be responsible for SJS which is also an immune mediated injury. The protozoan *Blastocystis* could induce an active inflammation and recruitment of the immunoregulatory cells.

This network of inflammatory cells could trigger the release of histamine releasing factors with mast cells degranulation which can further activate the immune response. Or it might be possible that *Blastocystis* toxin could activate complement pathway leading to release of histamine from mast cells and basophils causing related skin symptoms (Valsecchi *et al.*, 2004).

Treatment for *Blastocystis* spp. is still debatable due to ubiquitous and self-limiting nature of the parasite. Symptomatic cases and those with skin manifestations are usually recommended for treatment (Coyle *et al.*, 2011). In the present case however, despite considerable parasite burden and symptoms, medication was not required due to self-limiting nature of diarrhea and late diagnosis of the parasite in stool. A previous report on this aspect had commented that the allergic cutaneous lesions associated with *Blastocyctis* spp. might resolve after eradication of the parasite from the intestine (Coyle *et al.*, 2011).

Enteric colonization and infections of the protozoans in the children is very common especially in a developing country with low socio-economic condition. *Blastocystis* can be a harmful opportunistic pathogen in immune-compromised hosts. Thus, repeated screening of the stool samples for the presence of this parasite is necessary. *Blastocystis* is an emerging pathogen and as per the increasing reports of its pathogenic potential, its presence in stool sample should always be reported. Clinicians should be aware of the importance of routine stool examination for parasites in patients with SJS and acute diarrhea. The increasing pathogenic paradigm of *Blastocystis* is a threat and this report emphasizes the importance and recognition of newer insights of this pathogen.

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REFERENCES

Balint, A., Doczi, I., Bereczki, L., Gyulai, R., Szucs, M., Farkas, K. & Molnar, T. (2014). Do not forget the stool examination! – cutaneous and gastrointestinal manifestations of *Blastocystis* sp. infection. *Parasitology Research* **113**: 1585-1590.

Carbajal, J.A., Villar, J., Lanuza, M.D., Esteban, J.G., Munoz, C. & Borras, R. (1997). Clinical significance of Blastocystis hominis infection: epidemiologic study. *Medicina Clinica* **108**: 608-612.

Chen, T.L., Chan, C.C., Chen, H.P., Fung, C.P., Lin, C.P., Chan, W.L. & Liu, C.Y. (2003). Clinical characteristics and endoscopic findings associated with *Blastocystis hominis* in healthy adults. *The American Journal of Tropical Medicine and Hygiene* **69**: 213-216.

Clark, C.G., van der Giezen, M., Alfellani, M.A. & Stensvold, C.R. (2013). Recent developments in Blastocystis research. In *Advances in Parasitology*, Academic Press **82**, pp. 1-32.

Coyle, C.M., Varughese, J., Weiss, L.M. & Tanowitz, H.B. (2011). Blastocystis: to treat or not to treat. *Clinical Infectious Diseases* **54**: 105-110.

Das, R., Khalil, S., Mirdha, B.R., Makharia, G.K., Dattagupta, S. & Chaudhry, R. (2016). Molecular characterization and subtyping of Blastocystis species in irritable bowel syndrome patients from North India. *PLoS One* **11**: e0147055.

El Safadi, D., Gaayeb, L., Meloni, D., Cian, A., Poirier, P., Wawrzyniak, I., Delbac, F., Dabboussi, F., Delhaes, L., Seck, M. & Hamze, M. (2014). Children of Senegal River Basin show the highest prevalence of *Blastocystis* sp. ever observed worldwide. *BMC Infectious Diseases* **14**: 164.

Foster, C.S., Parillo, S.J., Letko, E., Ba-Abbad, R., Roy, H. Sr. (2015). Stevens-Johnson syndrome. Available at: http://emedicine.medscape.com/article/1197450-overview. Accessed January 7, 2018.

Kick, G., Rueff, F. & Przybilla, B. (2002). Palmoplantar pruritus subsiding after Blastocystis hominis eradication. *Acta Dermato-Venereologica* **82**: 60-60.

Kolkhir, P., Balakirski, G., Merk, H.F., Olisova, O. & Maurer, M. (2016). Chronic spontaneous urticaria and internal parasites–a systematic review. *Allergy* **71**: 308-322.

Kurniawan, A., Karyadi, T., Dwintasari, S.W., Sari, I.P., Yunihastuti, E., Djauzi, S. & Smith, H.V. (2009). Intestinal parasitic infections in HIV/AIDS patients presenting with diarrhoea in Jakarta, Indonesia. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **103**: 892-898.

Mirza, H. & Tan, K.S. (2012). Clinical aspects of *Blastocystis* infections: advancements amidst controversies. In *Blastocystis: Pathogen or Passenger?* Springer, Berlin, Heidelberg, pp. 65-84.

Noureldin, M.S., Shaltout, A.A., El, E.H. & Ali, M.E. (1999). Opportunistic intestinal protozoal infections in immune-compromised children. *Journal of the Egyptian Society of Parasitology* **29**: 951-961.

Salvador, F., Sulleiro, E., Sánchez-Montalvá, A., Alonso, C., Santos, J., Fuentes, I. & Molina, I. (2016). Epidemiological and clinical profile of adult patients with *Blastocystis* sp. infection in Barcelona, Spain. *Parasites & Vectors* **9**: 548.

Tan, T.C. & Suresh, K.G. (2006). Predominance of amoeboid forms of *Blastocystis hominis* in isolates from symptomatic patients. *Parasitology Research* **98**: 189-193.

Tan, K.S. (2008). New insights on classification, identification, and clinical relevance of *Blastocystis* spp. *Clinical Microbiology Reviews* **21**: 639-665.

Tasova, Y., Sahin, B., Koltas, S. & Paydas, S. (2000). Clinical significance and frequency of *Blastocystis hominis* in Turkish patients with hematological malignancy. *Acta Medica Okayama* **54**: 133-136.

Valsecchi, R., Leghissa, P. & Greco, V. (2004). Cutaneous lesions in *Blastocystis hominis* infection. *Acta Dermato Venereologica-Stockholm* **84**: 322-323.

Yang, M.S., Lee, J.Y., Kim, J., Kim, G.W., Kim, B.K., Kim, J.Y. & Kang, H.R. (2016). Incidence of Stevens-Johnson Syndrome and toxic epidermal necrolysis: a nationwide population-based study using National Health Insurance database in Korea. *PloS One* **11**: e0165933.

Yoshikawa, H., Abe, N., Iwasawa, M., Kitano, S., Nagano, I., Wu, Z. & Takahashi, Y. (2000). Genomic analysis of *Blastocystis hominis* Strains isolated from two long-term health care facilities. *Journal of Clinical Microbiology* **38**: 1324-1330.

Zaglool, D.A.M., Khodari, Y.A.W. & Farooq, M.U. (2012). *Blastocystis hominis* and allergic skin diseases; a single centre experience. *Journal of Health Sciences* **2**: 66-69.