Schistosoma mansoni infection is associated with increased monocytes and fewer natural killer T cells in the female genital tract

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BRIEF REPORT

Schistosoma mansoni Infection Is Associated With Increased Monocytes and Fewer Natural Killer T Cells in the Female Genital Tract

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Schistosoma mansoni infection may impair genital mucosal antiviral immunity, but immune cell populations have not been well characterized. We characterized mononuclear cells from cervical brushings of women with and without *S mansoni* infection. We observed lower frequencies of natural killer T cells and higher frequencies of $CD14^+$ monocytes in infected women.

Keywords. female urogenital schistosomiasis; monocytes; *Schistosoma mansoni*; schistosomiasis; women.

Schistosomiasis is a neglected parasitic infection affecting 250 million people worldwide [1,2]. *Schistosoma mansoni* infection, prevalent in sub-Saharan Africa [3], is associated with gastrointestinal and liver injury through direct and immune-mediated mechanisms [4]. However, less attention has focused on genital tract effects of *S. mansoni*.

Population-based and autopsy studies have established that *S. mansoni* eggs can be found in female genital tissue, particularly the cervix and vagina [5–9]. Several studies have reported a possible increased susceptibility to human immunodeficiency virus (HIV), or increased HIV viral entry into cervical cells, among women with *S. mansoni* infection, implying that cervical immune alterations may be associated with infection [10–13]. Furthermore, treatment of *S. mansoni* reduced entry of HIV into cervical $CD4^+$ T cells [10]. How *S. mansoni* alters the cervical immune compartment and mechanisms by which *S. mansoni* could impair genital mucosal antiviral immunity have been minimally investigated. Understanding this interaction could provide insight into immune effects of *S. mansoni* in the genital tract and help explain disparities in viral infections in women in countries where schistosomiasis is endemic [13].

Available limited human data suggest that schistosome infection could alter mucosal immune cell populations in the female genital tract, but these have not been well characterized in *S. mansoni* infection [14,15]. In mouse models, infection with *S. mansoni* or other helminths decreased subsequent mucosal cytotoxic $CD8^+$ T-cell responses to viruses in gastrointestinal mucosa [16,17]. Further murine studies indicate that alternatively activated type 2 (immunomodulatory) macrophages play a major role in the tissue immune response to *S. mansoni* eggs by promoting tissue granuloma formation and fibrosis, while concomitantly decreasing proinflammatory type 1 antiviral responses [18–20]. Notably, mouse models have focused on gastrointestinal and not genital mucosa.

To characterize genital immune cell composition in human *S. mansoni* infection, we studied mononuclear cells from cervical brushings of women with and without *S. mansoni* infection in Tanzania. We hypothesized that women with *S. mansoni* infection would have altered cervical immune cell frequencies compared to uninfected women, and we particularly focused on immune cells that may play a role in the antiviral mucosal immune response including natural killer (NK) cells, NK T cells, cytotoxic $CD8^+$ cells, and monocytes. Our goal was to identify alterations in cervical immune cells and potential therapeutic targets that could restore genital mucosal abnormalities that persist despite antiparasitic treatment [21].

METHODS

Overview

We studied baseline cervical samples from women aged 18–50 years participating in a longitudinal study in Tanzania in 2017. The study, conducted in rural communities near Lake Victoria among women who had limited access to clean water, has been previously described [22]. In brief, women provided written informed consent and underwent voluntary counseling and testing for HIV and screening for schistosome infection via egg detection in urine and stool, and circulating anodic antigen

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(CAA) testing in serum. Women who were HIV uninfected and had confirmed *S. mansoni* infection with stool eggs and serum CAA ≥30 pg/mL were invited to participate. A similar number of women without schistosome infection (egg negative and serum CAA <30 pg/mL) were also invited. In these communities, the prevalence of *S. mansoni* infection among adult women ranges from approximately 35% to 80%, while the prevalence of *Schistosoma haematobium* is approximately 2% [23–25]. See the Supplementary Appendix for details.

Cervical Mononuclear Cell Collection

Cervical mononuclear cells were collected during gynecologic examination using 2 endocervical cytobrushes and 1 Ayer spatula rotated 360° around the face of the os [26,27]. Cells were placed in phosphate-buffered saline (PBS), transported to Tanzania's National Institute for Medical Research laboratory within 4 hours of collection, vortexed, and the Ayer spatula discarded. Cytobrushes were scraped into a 15-mL Falcon tube using a 25-mL pipette while discharging PBS, as previously described with minor modifications [26]. Cells were washed, resuspended in 20% dimethyl sulfoxide, and cooled to −80°C using CoolCell (Corning), then to −156°C. Samples were shipped to Weill Cornell in New York at −150°C and stored in liquid nitrogen.

Flow Cytometry

Cells were washed twice in media containing 20% fetal bovine serum in RPMI and resuspended in 1 mL of the same media. Cells were then washed with Stain Buffer (BD Pharmigen) and incubated with Fc Receptor Blocking Solution (Biolegend) for 5 minutes. Cells were stained for 30 minutes in the dark with the following antibodies: CD14 PE, CD8 perCP-Cy5.5, CD56 PE-Dazzle 594, CD19 APC, CD4 PE-Cy7, CD45 Alexa700, CD3 BV711, and DAPI (all Biolegend). Compensation controls were prepared using UltraComp eBeads (Thermo Fisher). Cells and beads were then washed and resuspended in Stain Buffer (BD Pharmigen).

Flow cytometry was performed using a BD LSR Fortessa flow cytometer, equipped with 355-, 405-, 488-, 561-, and 640-nm lasers, in Weill Cornell's Flow Cytometry Core. Cleaning and gating were performed using FlowJo (BD). Fluorescence Minus One controls using healthy-donor peripheral blood mononuclear cells were created to obtain reliable gating parameters. A gating strategy was used to define 11 cell types, all derived from a parent $DAPI^-/CD45^+$ gate (Supplementary Table 1). A subset of samples underwent additional staining and gating that included markers for neutrophils, eosinophils, and basophils (Supplementary Table 2).

Statistical Analyses

Analyses were performed using Stata 15.1 (StataCorp). We summarized continuous variables with median and interquartile range [IQR] and categorical variables with numbers and percentages. We used rank-sum tests to compare median values between participants, including percentages of cell types out of total $CD45^+$ cells. We compared categorical variables using Fisher exact or χ^2 tests where appropriate.

Table 1. Clinical and Sociodemographic Characteristics of 33 Women With and Without *Schistosoma mansoni* Infection

Characteristic	*S. mansoni* Infected (n = 13)	Uninfected (n = 20)	*P* Value
Age, y, median (IQR) (n = 32)	27 (23–38)	30 (24–30)	.73
Marital status (n = 32)			.71
Single	2 (15.4)	1 (5.3)	
Married	9 (69.2)	14 (73.7)	
Divorced	2 (15.4)	4 (21)	
In the last month, did not eat lunch or dinner due to shortage of food (n = 32)	10 (76.9)	9 (47.4)	.09
Years attended school, median (IQR) (n = 32)	7 (4–7)	7 (4–7)	.83
No. of days since last menstrual period, median (IQR)	15 (14–15)	11 (10–15)	.37
Children birthed, median (IQR) (n = 32)	3 (2–4)	3 (2–6)	.613
In the last year, tried to get pregnant without succeeding (n = 32)	2 (15.4)	3 (15.8)	1.00
All children have the same father (n = 30)	4 (33.3)	17 (94.4)	.001
Ever treated for schistosomiasis (n = 32)	2 (15.4)	8 (42)	.11
Previously treated for STIs, genital discharge, genital itching, or another infection in the genital area (n = 31)	7 (53.8)	7 (38.9)	.41
Pain during sex in the past year (n = 30)	6 (46.1)	9 (52.9)	.71
Bleeding after sex in the past year (n = 30)	3 (27.3)	1 (5.3)	.13
Painful genital ulcers in the past year (n = 32)	6 (45.1)	5 (26.3)	.246
Nonpainful genital ulcers in the past year (n = 32)	5 (38.5)	5 (26.3)	.47
Genital warts in the past year (n = 32)	5 (38.5)	12 (63.2)	.17
Condom use in the past 3 mo (n = 31)	7 (53.8)	5 (27.8)	.14
Contraceptive use in the form of injections, implants, or an IUD in the past 3 mo (n = 32)	5 (38.5)	6 (31.6)	.69
Cleaned inside the vagina with soap or soap and water in the past 3 mo (n = 32)	9 (69.2)	15 (78.9)	.53
Frequency of cleansing inside the vagina each week for the past 3 mo, median (IQR)	7 (2–14)	7 (7–14)	1
Serum CAA, pg/mL, median (IQR)	1527.1 (635.7–4680)	2.1 (0–6.3)	[a]
Stool egg count, eggs/g, median (IQR)	19.2 (9.6–43.2)	0 (0–0)	[a]
Trichomoniasis (n = 30)	2 (18.2)	5 (26.3)	1
Gonorrhea	1 (7.7)	1 (5)	1
Chlamydia	0	2 (10)	.24
Acetowhite lesions seen during acetic acid screening	0	2 (10)	.51

Data are reported as No. (%) unless otherwise noted.

Abbreviations: CAA, circulating anodic antigen; IQR, interquartile range; IUD, intrauterine device; STI, sexually transmitted infection.

[a]Included in study definition; *P* value not calculated.

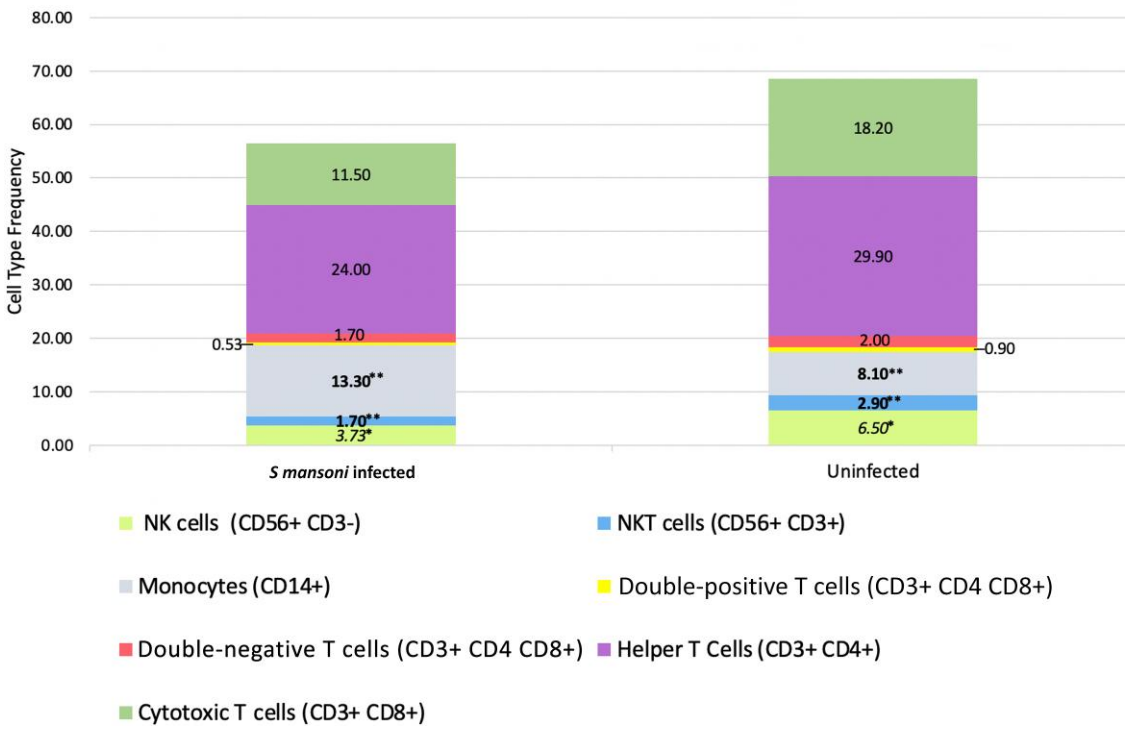

Figure 1. Cervical mononuclear cell types in women with and without *Schistosoma mansoni* infection. Bar graph containing median frequencies of cervical mononuclear cell types (as percentage of $CD45^+DAPI^-$ cells) in women with (n = 13) and without (n = 20) *S. mansoni* infection. Cell types quantified include monocytes, T-cell subsets, natural killer (NK) cells, and natural killer T (NKT) cells. Differences between frequencies: $^*P < .10$, $^{**}P < .05$.

Patient Consent Statement

All participants provided written informed consent, with ethical approvals obtained in New York and Tanzania (Supplementary Appendix).

RESULTS

Participant Characteristics

Sixty-four cervical samples were available for testing. Of these, 31 had <1000 viable $CD45^+$ cells and were excluded. The remaining 33 samples included in the analysis had a median $CD45^+$ cell count of 6067 total cells [IQR, 3130–12 586]. Among these 33 women, 13 (39%) had *S. mansoni* infection. Most factors were similar between those with *S. mansoni* and those without (Table 1). Women with *S. mansoni* infection had a median serum CAA of 1527.1 [IQR, 635.7–4680] pg/mL and 19.2 [IQR, 9.6–43.2] eggs per gram of stool. No differences were noted between the 31 women excluded for insufficient $CD45^+$ cells and the 33 who were included (Supplementary Table 3).

Cervical Mononuclear Cell Frequencies

Natural killer T cells ($CD56^+CD3^+$) were less frequent among women with *S. mansoni* infection than those without (median 1.7% [IQR, 1%–2.8%] vs 2.9% [2.0%–6.6%], $P = .017$; Figure 1). A similar trend was observed among NK cells ($CD56^+CD3^-$: 3.7% [2.6%–6.5%] vs 6.5% [4.5%–9.9%], $P = .065$). Women with *S. mansoni* also had higher frequencies of $CD14^+$ monocytes (13.3% [9.8%–29%] vs 8.1% [3.7%–18.4%], $P = .03$). No differences in other cell type frequencies, including cytotoxic $CD8^+$ T cells or helper $CD4^+$ T cells, were noted.

A subset of 8 women with *S. mansoni* infection and 14 without had additional neutrophil, eosinophil, and basophil markers included. Frequencies of these cells did not differ by *S. mansoni* infection status (Supplementary Figure 1).

DISCUSSION

We report that the human cervical immune compartment is altered in *S. mansoni* infection. These data align with prior studies in mice and humans demonstrating that helminth infections could cause mucosal immune dysregulation, which in *S. mansoni* infection was associated with increased HIV viral entry [10,16,17,28]. Specifically, we found lower NK T cells, a trend toward lower NK cells, and increased $CD14^+$ monocytes in *S. mansoni* infection. We note our focus on *S. mansoni* infection, not classically regarded as having urogenital effects, in genital mucosal immune populations.

Our findings point in the same direction as observations of increased viral infection and impaired genital antiviral immunity in women with *S. mansoni*. Lower NKT and NK cell frequencies could reduce mucosal antiviral immunity. Given that NKT cell proliferation is often accompanied and promoted by interferon secretion [29,30], these findings are in agreement with previously reported dysregulated interferon secretion from cervical cells of Kenyan women with *S. mansoni* [10]. Similarly, increased $CD14^+$ monocytes, particularly if they represent an increase in the type 2 to type 1 monocyte ratio, would also be expected to decrease mucosal antiviral immunity [16,18]. Together with observations of schistosomes impairing host immunity to a variety of viral infections [13], our data could indicate clinically meaningful pathways by which schistosome infection may impair control of viral infections in the genital mucosa.

Our data supplement only 2 other studies of cervical mucosal immune cells in schistosome infections. In the eloquent Kenyan study described above, investigators reported no change in $CD4^+$ cervical cells pre- and posttreatment for *S. mansoni*, but did not describe other cervical mononuclear populations. A study of South African women with *S. haematobium* infection reported decreased frequency of cervical $CD14^+$ cells following praziquantel treatment, which could be consistent with our findings of increased $CD14^+$ cells at baseline [15]. This South African study reported that <2% of cervical mononuclear cells were $CD14^+$, contrasting with findings from our study and others that $CD14^+$ cells constitute 10%–30% of mononuclear cells [15,26,31]. We confirm findings from these studies regarding pretreatment $CD4^+$ and $CD14^+$ frequencies, and add data on lower NK and NKT cell frequencies in *S. mansoni* infection.

This study had strengths and limitations. It is the first to quantify the proportions of genital immune cells broadly in relation to schistosome infection. As in many cervical cell isolation studies, approximately one-half of study samples had insufficient cell numbers for stringent analysis and were excluded, limiting sample size. Furthermore, we were limited to few cell surface markers given flow cytometry capabilities; future studies incorporating more advanced techniques such as spectral flow or mass cytometry could further characterize $CD14^+$ monocytes and quantify other cells of interest such as regulatory T and dendritic cells.

Future longitudinal studies to quantify effects of *S. mansoni* on genital mucosal immune cell populations, both before and after treatment, are needed. Such analysis will identify persistent alterations and point toward targeted therapies, potentially including host-directed immunomodulatory agents, that could be combined with praziquantel to promote mucosal healing in women suffering from genital tract sequelae of schistosome infections.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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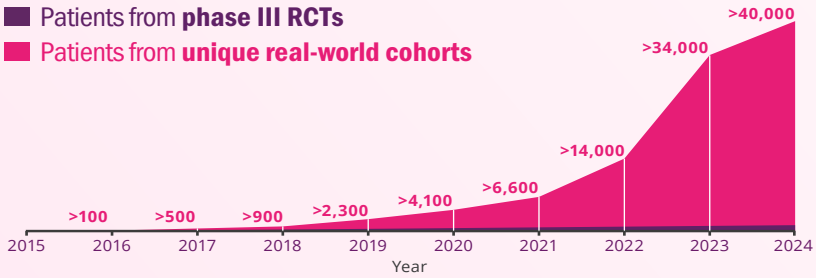

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ABBREVIATIONS

3TC, lamivudine; **CD4,** cluster of differentiation 4; **DTG,** dolutegravir; **FDA,** United States Food and Drug Administration; **FTC,** emtricitabine; **HIV,** human immunodeficiency virus; **ITT-E,** intention-to-treat exposed; **NRTI,** nucleoside/nucleotide reverse transcriptase inhibitor; **RCT,** randomised controlled trial; **RNA,** ribonucleic acid; **TAF,** tenofovir alafenamide fumarate; **TDF,** tenofovir disoproxil fumarate; **XTC,** emtricitabine.

FOOTNOTES

*Data extracted from a systematic literature review of DTG+3TC real-world evidence. Overlap between cohorts cannot be fully excluded.

**The reported rate reflects the sum-total of resistance cases calculated from GEMINI I and II (n=1/716, through 144 weeks), STAT (n=0/131, through 52 weeks), and D2ARLING (n=0/106, through 24 weeks).[5–7]

†GEMINI I and II are two identical 148-week, phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority, controlled clinical trials testing the efficacy of DTG/3TC in treatment-naïve patients. Participants with screening HIV-1 RNA ≤500,000 copies/mL were randomised 1:1 to once-daily DTG/3TC (n=716, pooled) or DTG + TDF/FTC (n=717, pooled). The primary endpoint of each GEMINI study was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).[13]

‡STAT is a phase IIIb, open-label, 48-week, single-arm pilot study evaluating the feasibility, efficacy, and safety of DTG/3TC in 131 newly diagnosed HIV-1 infected adults as a first line regimen. The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 24.[6]

§D2ARLING is a randomised, open-label, phase IV study designed to assess the efficacy and safety of DTG/3TC in treatment-naïve people with HIV with no available baseline HIV-1 resistance testing. Participants were randomised in a 1:1 ratio to receive DTG/3TC (n=106) or DTG + TDF/XTC (n=108). The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48.[7] Results at week 24 of the study.

||The reported rate reflects the sum-total of resistance cases calculated from TANGO (n=0/369, through 196 weeks) and SALSA (n=0/246, through 48 weeks).[8,9]

¶TANGO is a randomised, open-label, trial testing the efficacy of DOVATO in virologically suppressed patients. Participants were randomised in a 1:1 ratio to receive DOVATO (n=369) or continue with TAF-containing regimens (n=372) for up to 200 weeks. At Week 148, 298 of those on TAF-based regimens switched to DOVATO. The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL (virologic non-response) as per the FDA Snapshot category at Week 48 (adjusted for randomisation stratification factor).[8,13]

#SALSA is a phase III, randomised, open-label, non-inferiority clinical trial evaluating the efficacy and safety of switching to DTG/3TC compared with continuing current antiretroviral regimens in virologically suppressed adults with HIV. Eligible participants were randomised 1:1 to switch to once-daily DTG/3TC (n=246) or continue current antiretroviral regimens (n=247). The primary endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).[9]

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