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International travelers with infectious diseases determined by pathology results, Centers for Disease Control and Prevention — United States, 1995–2015

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Abstract

Background—The failure to consider travel-related diagnoses, the lack of diagnostic capacity for specialized laboratory testing, and the declining number of autopsies may affect the diagnosis and management of travel-related infections. Pre- and post-mortem pathology can help determine causes of illness and death in international travelers.

Methods—We conducted a retrospective review of biopsy and autopsy specimens sent to the Infectious Diseases Pathology Branch laboratory (IDPBL) at the Centers for Disease Control and Prevention (CDC) for diagnostic testing from 1995 through 2015. Cases were included if the specimen submitted for diagnosis was from a traveler with prior international travel during the disease incubation period and the cause of illness or death was unknown at the time of specimen submission.

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Declarations

This project was designated nonresearch by a CDC human subjects advisor. None of the authors reported any conflicts of interest.

Author contributions

Kristina M. Angelo: Primary writer, primary contributor to data interpretation.
Kira Barbre: Secondary writer, contributor to data interpretation.
Wun-Ju Shieh: Supplied case study information, provided pathologic explanations for the images and manuscript, technical editing, contributor to data interpretation.
Phyllis E. Kozarsky: Critical manuscript revision and writing, technical editing, contributor to data interpretation.
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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the United States Centers for Disease Control and Prevention.

Results—Twenty-one travelers, six (29%) with biopsy specimens and 15 (71%) with autopsy specimens, met the inclusion criteria. Among the 15 travelers who underwent autopsies, the most common diagnoses were protozoal infections (7 travelers; 47%), including five malaria cases, followed by viral infections (6 travelers; 40%).

Conclusions—Biopsy or autopsy specimens can assist in diagnosing infectious diseases in travelers, especially from pathogens not endemic in the U.S. CDC's IDPBL provides a useful resource for clinicians considering infectious diseases in returned travelers.

Keywords

Pathology; Autopsy; International; Travel; Biopsy

1. Introduction

International travel has expanded over the past 50 years. In 2012, annual worldwide international tourist arrivals exceeded one billion, and arrivals will likely reach 1.8 billion by 2030 [1]. Travel destinations continue to diversify, with emerging economies accounting for approximately 533 million tourist arrivals in 2015 [1]. These trends bring more travelers into contact with infectious pathogens, which can have serious individual and public health consequences and can contribute to infectious disease spread [2].

Travelers often acquire infections while abroad, most commonly a gastrointestinal or systemic febrile illness [3]. However, an etiology to explain the travelers' symptoms may not always be determined in the clinical setting. Ill travelers may require non-routine laboratory or pathology services, including special serologies or biopsies, to confirm a diagnosis and guide effective treatment and public health interventions. In addition, healthcare providers in non-endemic countries may fail to consider travel-related diagnoses such as malaria, leading to delays in treatment, or death. Healthcare providers should take detailed travel histories and have increased suspicion for travel-related infections, using available diagnostic tests as appropriate. Specialized pathological biopsy and autopsy specimen testing provide useful information about causes of undetermined illness and death in travelers [4] and can expedite appropriate treatment. Published data on the total number of deaths due to infectious diseases acquired while traveling abroad is lacking.

We present clinical vignettes and final infectious diseases diagnoses of 21 international travelers with either biopsy or autopsy specimens sent to the Infectious Diseases Pathology Branch Laboratory (IDPBL) at the Centers for Disease Control and Prevention (CDC) for diagnostic assistance of unexplained illnesses and deaths. The IDPBL applies histological, immunohistochemical, molecular, microbiologic, and ultrastructural methodologies to uncover infectious disease diagnoses on tissue specimens or cultures and is available to domestic and international clinicians, hospital systems, and health departments [5].

2. Methods

We conducted a retrospective review of autopsy and biopsy specimens sent to CDC's IDPBL for diagnostic testing from 1995 through 2015. Cases were included if the specimen was

from an international traveler, the cause of illness or death was unknown at the time of specimen submission, and travel was during the disease incubation period. Clinicians and pathologists submitted assorted information extracted from the travelers' medical record. We reviewed all available information and recorded traveler demographics, travel destination, travel purpose, reported exposures or behaviors during travel, presumptive clinical diagnoses, and clinical course details, including outcome.

3. Results

Twenty-one travelers met the inclusion criteria (Table 1). Median age was 38 years (range 2–73), 43% were female, and 15 (71%) were U.S. residents. Twelve (57%) contracted their illness in Sub-Saharan Africa; other exposure regions included Central America (two travelers), South America (two travelers), Asia (one traveler), the Caribbean (one traveler), the Middle East (one traveler), North America (one traveler), and Oceania (one traveler). Six (29%) had biopsy specimens and 15 (71%) had autopsy specimens sent to the IDPBL.

3.1. Travelers with biopsies

Among the six travelers with biopsy specimens, five had cutaneous specimens and one had an open lung biopsy specimen; none died (Table 1).

Traveler 1 (2008)—A 58-year-old female had a scalp lesion biopsied after returning to the United States from Belize. Gross examination confirmed myiasis with the botfly *Dermatobia hominis* (Fig. 1A).

Traveler 2 (2011)—U.S. immigration officials detained a 62-year-old female with extensive face and upper-extremity skin lesions after returning from an 8-week missionary trip to rural Ghana. Tissue Gram stain on skin biopsy specimens sent to the IDPBL yielded Gram-positive cocci, and immunohistochemistry (IHC) demonstrated group A *streptococci* among diffuse neutrophilic infiltrates with epithelial necrosis, consistent with impetigo (Fig. 1B and C).

Traveler 3 (2011)—A 59-year-old male developed fever, myalgia, arthralgia, non-productive cough, hemoptysis, and dyspnea on exertion after returning from a 1-week trip constructing homes in rural Panama. A chest radiograph and computed tomography scan of the chest revealed pulmonary lesions with mediastinal and hilar lymphadenopathy; he underwent an open lung biopsy. Tissue staining revealed multiple small budding yeasts; in conjunction with IHC and polymerase chain reaction (PCR), the IDPBL confirmed acute *Histoplasma capsulatum* pneumonia (Fig. 1D).

Traveler 4 (2012)—A 31-year-old male developed a painful, ulcerated leg lesion and fever while traveling in rural Papua New Guinea. An infectious diseases consultant suspected a Buruli ulcer caused by *Mycobacterium ulcerans*. A biopsy sent to IDPBL revealed a tropical phagedenic ulcer with necrotizing dermatitis, hemorrhage, edema and thrombosis, including a polymicrobial infection with *Fusobacterium nucleatum* and *Treponema vincentii.* The traveler underwent debridement and took cephalexin for 1 week, with lesion improvement.

Traveler 5 (2014)—A 39-year-old male sustained an insect bite on his leg that ulcerated a few months after returning from Peru. The lesion was biopsied and IHC revealed intra- and extracellular basophilic structures at the IDPBL, consistent with New World cutaneous leishmaniasis (Fig. 1E and F).

Traveler 6 (2015)—A 65-year-old female complained of headache, fevers, chills, myalgias, and an eschar on her left calf, where she recalled a tick bite. She recently returned from a 2-week trip to South Africa. Her physician prescribed doxycycline and submitted skin biopsy specimens to the IDPBL. IHC demonstrated epidermal ulceration with lymphohistiocytic inflammation, and PCR yielded *Rickettsia africae*, the causal agent of African tick bite fever (Fig. 1G and H).

3.2. Travelers with autopsies

Among the 15 travelers who underwent autopsies, the most common diagnoses were protozoal (7; 47%) and viral (6; 40%) infections. Ten (67%) traveled to Sub-Saharan Africa during their illness incubation periods.

3.2.1. Protozoal infections: malaria—Upon histological examination of multiple organs and identification of intraerythrocytic *Plasmodium falciparum* trophozoite and schizont staining patterns by IHC, the IDPBL diagnosed travelers 7–11 with fatal *P. falciparum* malaria.

Travelers 7 and 8 (1996): Two male (unknown ages) Romanian cargo ship workers in Sub-Saharan Africa died aboard their ship. They had recent port calls in Gabon, Guinea, and South Africa. Authorities suspected Ebola due to a concurrent outbreak in Gabon [6].

Traveler 9 (2004): A 36-year-old male cargo ship worker became ill with fever, chills, headache, myalgias, sore throat, nausea, vomiting, jaundice, and bloody urine. Clinicians suspected Lassa fever due to multiple recent port calls in West Africa (Nigeria, Sierra Leone, and Côte d'Ivoire). The traveler died while aboard; authorities detained the ship and crew offshore until autopsy results became available [6].

Traveler 10 (2005): A 43-year-old male complained of fever, cough, myalgias, arthralgias, and "dark urine" after returning from a 2-week missionary trip to the Central African Republic and Côte d'Ivoire. His clinician suspected yellow fever or dengue infection. He did not take malaria chemoprophylaxis. He died upon arrival to the hospital [6].

Traveler 11 (2011): A 4-year-old female complained of fever, cough, diarrhea, and vomiting while visiting friends and relatives in Uganda. She did not take malaria chemoprophylaxis. A physician in Uganda treated her for a bacterial infection and tested her for malaria, but she did not receive a confirmed diagnosis or malaria treatment. Her condition worsened and she died shortly after arrival in the United States [7]. (Fig. 2A).

3.2.2. Protozoal infections: other

Traveler 12 (2009): A 30-year-old female Sudanese refugee became ill with acute leukemia after arriving in the United States from Kenya. She developed severe cardiac failure 2 months after receiving a bone marrow transplant and died. Cardiac tissue sent to the IDPBL indicated myocarditis with protozoal organisms consistent with *Sarcocystis* spp, confirmed by PCR (Fig. 2B).

Traveler 13 (2011): A 2-year-old male became ill with cough, rhinorrhea, and left hemiparesis after returning to the United States from Mexico. Brain imaging suggested neurocysticercosis; he received steroids and albendazole, without improvement. He developed seizures and died. Microscopic examination of brain biopsy specimens sent to the IDPBL revealed granulomatous inflammation with necrosis and amebic organisms highlighted with IHC (Fig. 2C and D). PCR confirmed infection with *Balamuthia mandrillaris*, a free-living ameba causing granulomatous amebic encephalitis.

3.2.3. Viral infections

Traveler 14 (1999): A 45-year-old male became ill after returning to the United States from a 10-day trip to Venezuela, where he swam in fresh water and visited the rainforest. He developed fulminant renal and liver failure and disseminated intravascular coagulation, complicated by an intracerebral hemorrhage, and died a few days after admission. Autopsy specimens sent to the IDPBL showed histopathologic changes with massive hepatocellular necrosis, and IHC confirmed the etiologic agent as yellow fever virus.

Traveler 15 (2004): A 38-year-old male Liberian-born U.S. resident became ill with fever, chills, sore throat, diarrhea, and back pain while visiting farms in Liberia and Sierra Leone. After returning to the United States, he clinically deteriorated with acute respiratory distress syndrome despite treatment for malaria and typhoid fever. IHC on liver biopsy specimens performed by the IDPBL were positive for Lassa virus. The result was further confirmed by serum antigen detection, virus isolation in cell culture, and virus identification by PCR on blood, liver, and skin specimens [8] (Fig. 2E and F).

Traveler 16 (2008): A 33-year-old Zambian male paramedic cared for a 36-year-old woman on a medical evacuation flight from Zambia to South Africa. The woman had a rash, facial swelling, and myalgia and received mechanical ventilation during the flight. The paramedic developed headache, myalgia, and fever six days after the flight and died. Blood, liver, and skin specimens underwent IHC testing, demonstrating scattered hepatocellular necrosis, and PCR revealed a novel Old World arenavirus, Lujo virus. The paramedic's infection was one of three secondary cases from nosocomial contact with the ill woman [9].

Traveler 17 (2010): A 12-year-old female became ill with headache, fever, nausea, vomiting, seizures, and altered mental status after returning to the United States from a 2-week trip to Manila, Philippines. She did not improve with treatment for bacterial meningitis and died. Brain biopsy specimens tested at both the state lab and IDPBL demonstrated meningoencephalitis with neuronal necrosis, neuronophagia, and glial nodules; PCR indicated infection with Japanese encephalitis virus.

Traveler 18 (2011): A 24-year-old male soldier deployed to Afghanistan sustained a dog bite to the right hand. He did not receive rabies post-exposure prophylaxis. He developed severe arm pain and right hand paresthesia while en-route to the United States, followed by progressive meningoencephalitis and death. Nuchal biopsy specimens, saliva, CSF, and autopsy brain samples underwent testing. Microscopic examination of the autopsy brain samples demonstrated Negri bodies, and IHC showed rabies viral antigens (Fig. 2 G–H). PCR confirmed rabies [10].

Traveler 19 (2011): A 73-year-old Haitian female developed right shoulder pain, headaches, and difficulty swallowing while visiting friends and relatives in the United States; she developed encephalitis and died. A nuchal skin biopsy sent to the CDC rabies laboratory demonstrated rabies antigens by direct fluorescent antibody testing, and a saliva specimen tested positive by PCR for rabies virus. Autopsy brain samples submitted to IDPBL showed Negri bodies, and IHC was positive for rabies virus. A dog bit the traveler in Haiti and she did not receive post-exposure prophylaxis [11].

3.2.4. Rickettsial infections

Traveler 20 (1995): A 38-year-old Swiss female nurse caring for ill prison inmates in Burundi developed fever, chills, and myalgias associated with severe thrombocytopenia. She received ciprofloxacin for presumed typhoid fever. Despite treatment, she died. Histopathologic examination of autopsy specimens sent to the IDPBL demonstrated vasculitis in multiple organs, and IHC was positive for typhus group rickettsiae. PCR further identified *Rickettsia prowazekii*, the causative agent of louse-borne epidemic typhus [12].

Traveler 21 (1999): A 39-year old female developed a furuncle on her left leg associated with fever, chills, myalgias, headache, and a generalized maculopapular rash while on a missionary trip in Kenya. Prior to her illness, her dog had “tick-borne fever” and improved. Despite receiving malaria treatment, her condition worsened. She developed a left leg eschar, in addition to thrombocytopenia (107,000/mm^3), and died. Microscopic examination of autopsy tissues showed vasculitis and microthrombi in multiple organs; IHC was positive for rickettsiae, but did not identify a species [13].

4. Discussion

We describe the pathologic diagnoses of travel-related illnesses using specialized diagnostic capacity from CDC’s IDPBL. These findings illustrate the importance of pathology diagnostics in identifying undiagnosed illness or death from infectious diseases. This is particularly important for the rising numbers of international travelers who may become ill with infections rare or non-endemic in the United States. It is also important for travel medicine clinicians who provide care to returned travelers, to utilize these resources for appropriate diagnosis and treatment.

Obtaining an autopsy from undiagnosed deceased individuals can provide useful information not only about causes of death in travelers, but also on illnesses not recognized clinically prior to death [4,14]. For example, an autopsy was recently instrumental in diagnosing the first measles death in the United States in 12 years [15]. Autopsies may decrease gaps in

surveillance, leading to enhanced infectious disease risk estimates, and result in more rapid diagnosis and treatment of contacts, as well as public health response. Despite the autopsy's value for determining cause of death, autopsy rates in the United States have declined significantly since the 1960s [4]. Prior to 1970, 40–60% of all hospital deaths in the United States received autopsies, but in recent years, decreased to approximately 5% [16]. Additionally, infectious diseases accounted for 46% of causes of death determined by autopsy in 2007, down from 79% in 1972 [14]. This may be due to improvement in infectious disease treatment, but also the relative decrease in medical autopsies and the relative increase in autopsies due to external causes (*e.g.*, firearms) [14]. This decline may also be due to cost constraints, clinicians seeking fewer autopsies, and the removal of the minimum autopsy rate mandate for hospitals by the Joint Commission on Accreditation for Healthcare Organizations in 1970 [17]. The declining number of medical autopsies has additional effects, such as a decrease in forensic autopsy experience for training pathologists, resulting in a lack of experience to recognize subtle findings, or decreased medical care quality assurance [17].

Among the 15 deaths, more than half were preventable through recommended pre-travel vaccination or chemoprophylaxis. Almost all deaths were potentially preventable through early diagnosis and treatment, including the five in travelers infected with *P. falciparum* malaria. The focus on alternative diagnoses, despite travel to a malaria-endemic area, resulted in diagnostic and treatment delays. Among the more than 1700 reported malaria infections among U.S. travelers in 2013, Africa was the most common exposure region, *P. falciparum* comprised the majority of infections, and there were 10 deaths [18]. Malaria must be on the differential diagnosis for febrile travelers with recent travel to a malaria-endemic country, and such travelers should visit a healthcare professional immediately if any malaria symptoms, such as fever, develop during or after travel.

It is imperative to obtain a travel history on all patients, especially those with a fever [3]. Clinicians should also note possible risky exposures (*e.g.*, animal, water, or insect exposures) in a travelers' itinerary. Rash was present in only 26%, and an eschar was present in 55% of U.S. travelers with spotted fever rickettsioses in one report [19], so reliance on the clinical examination and laboratories alone may not always result in a diagnosis.

This report provides details on pathology submissions sent the IDPBL for specialized testing that were shown to be travel-related; however, although only one case each of leishmaniasis and African tick bite fever are presented, the IDPBL received many traveler's skin biopsy specimens from clinicians concerned about these two diseases. The IDPBL identified *Leishmania* spp. in 370 of these biopsy specimens (CDC data, unpublished). Due to low sensitivity and specificity, serologic testing does not play a role in diagnosis; PCR or specialized tissue diagnostics are necessary. IDPBL also identified *Rickettsia africae* in 16 cutaneous biopsy specimens during the same timeframe; African tick bite fever is the most common rickettsiosis identified in travelers returning from Africa [19].

One potential limitation is that the clinical data submitted to the IDPBL for each traveler varied. Although we reviewed all available information and recorded traveler demographics, travel destination, travel purpose, reported exposures or behaviors during travel, presumptive

clinical diagnoses, and clinical course details, including outcome, this information may not have been available for all travelers. Efforts are forthcoming to standardize the clinical information sent with submitted specimens. An additional limitation is that clinicians may opt to submit specimens to the IDPBL based upon the lack of availability of diagnostic testing in their institutions or health departments, and the frequency of submission may vary by the type of clinical site (and their specialization) or country.

CDC is committed to promoting pathogen detection through laboratory-based diagnostics, modern point-of-care testing, and facilitation of specimen submission to public health reference laboratories [20]. Access to appropriate diagnostic tests may expedite diagnosis and treatment of travelers with infectious diseases. CDC's IDPBL has the capability to perform specialized diagnostic testing to help diagnose unexplained deaths among international travelers, and providers are encouraged to use this service (pathology@cdc.gov) when encountering difficult cases.

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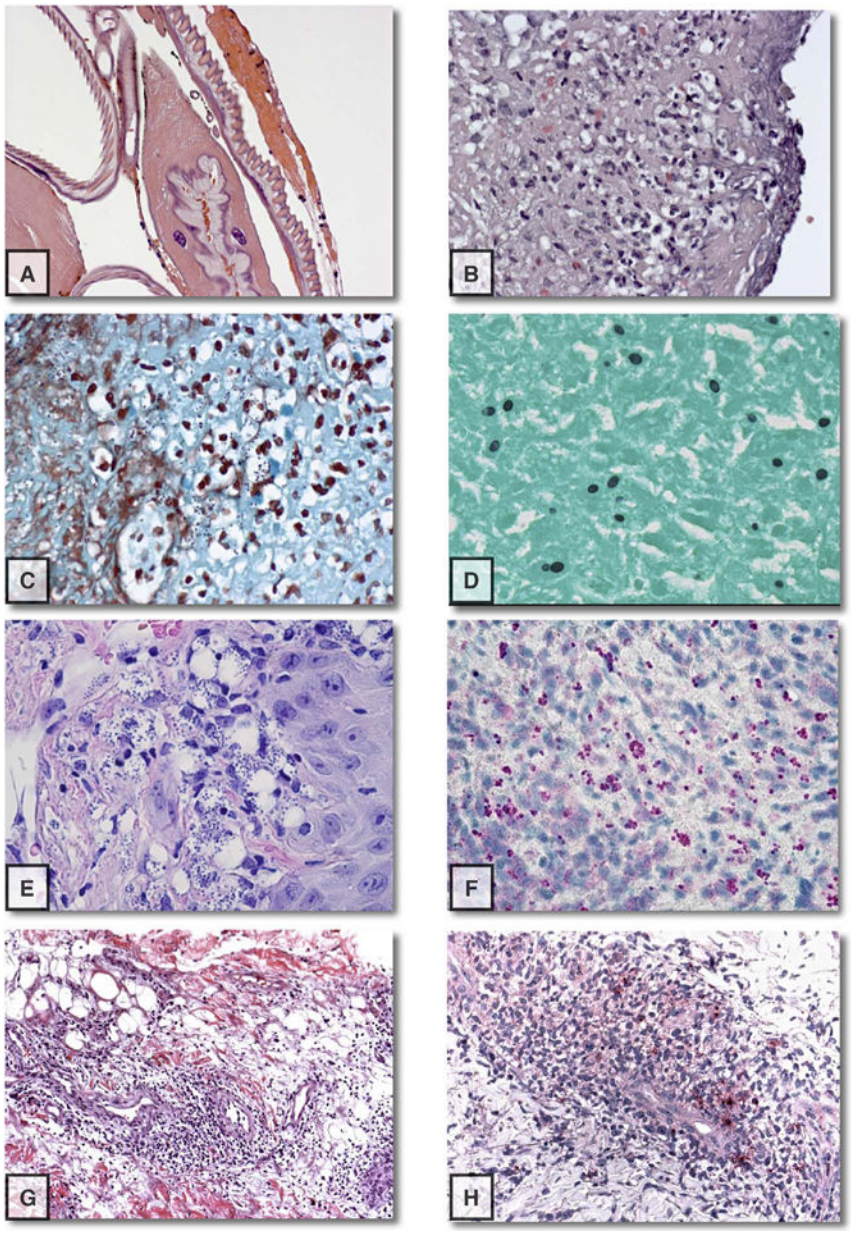

Fig. 1.

Histopathologic findings of biopsy and autopsy specimens from international travelers submitted to the Centers for Disease Control and Prevention's Infectious Diseases Pathology Branch laboratory, 1995–2015. **A)** Traveler 1: *Dermatobia hominis* myiasis. Microscopic examination demonstrating the cuticle, striated muscles, and spiracles of the larva; H & E staining, original magnification: ×200. **B–C)** Traveler 2: Group A *Streptococcus* impetigo. B) Skin biopsy demonstrates epidermal ulceration and neutrophilic infiltrate in dermis; H & E staining, original magnification: ×200. C) Numerous gram-positive cocci in the dermis admixed with neutrophils; Lillie-Twort Gram staining, original magnification: ×400. **D)** Traveler 3: Acute pulmonary histoplasmosis. Lung biopsy demonstrating necrotizing inflammation with multiple yeast organisms, some with budding feature; Grocott's

methenamine-silver staining, original magnification: ×400. **E**–**F)** Traveler 5: Cutaneous leishmaniasis. E) Skin biopsy demonstrates lymphohistiocytic infiltrates in dermis with abundant intra- and extracellular round basophilic structures; H & E staining, original magnification: ×400. F) Immunostaining of *Leishmania* species in dermis; immunoalkaline phosphate staining, naphthol fast red substrate with light hematoxylin counterstain, original magnification: ×400. **G**–**H)** Traveler 6: African tick-bite fever. G) Skin biopsy demonstrates leukocytoclastic vasculitis and perivascular lymphohistiocytic infiltrate; H & E staining, original magnification: ×200. H) Immunostaining of spotted fever group rickettsiae in the vascular wall and perivascular infiltrates; immunoalkaline phosphate staining, naphthol fast red substrate with light hematoxylin counterstain, original magnification: ×400.

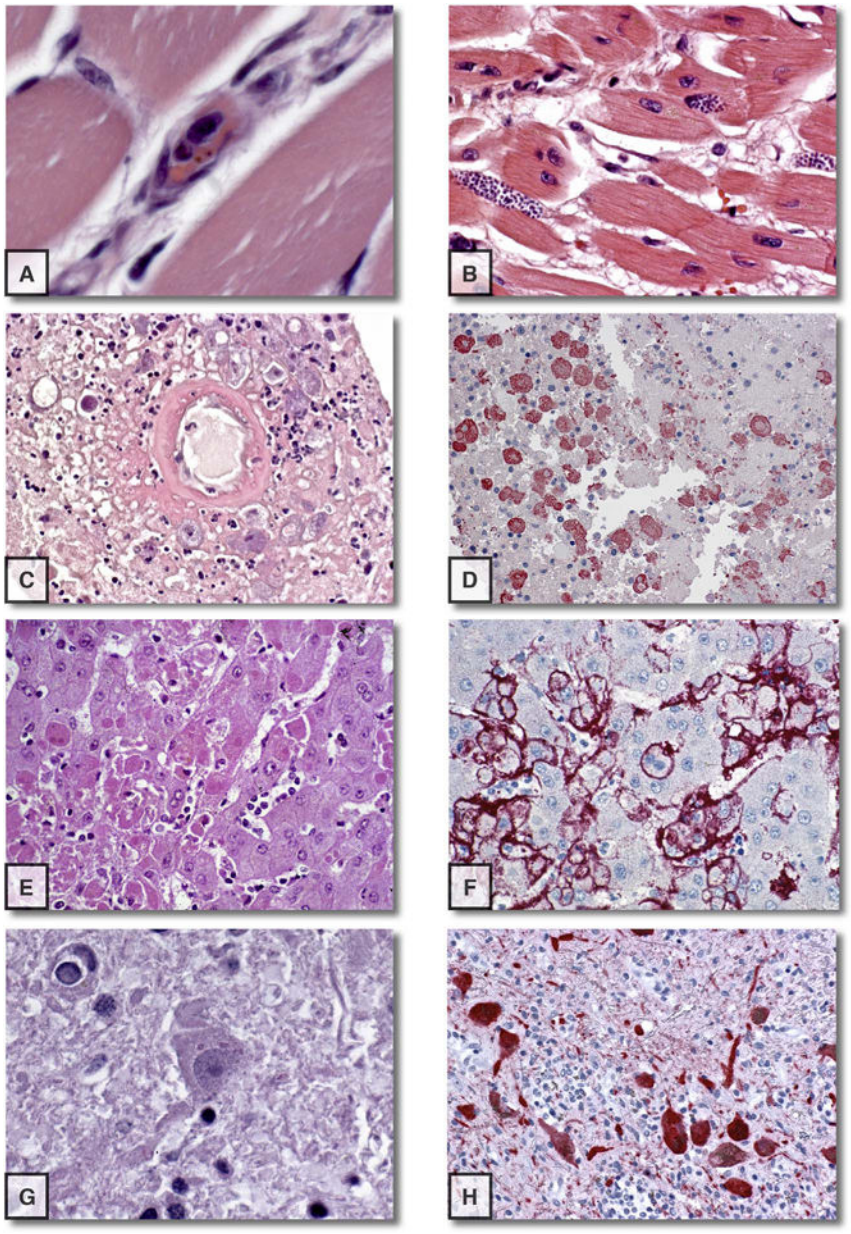

Fig. 2.

Histopathologic findings of biopsy and autopsy specimens from international travelers submitted to the Centers for Disease Control and Prevention's Infectious Diseases Pathology Branch laboratory, 1995–2015. **A)** Traveler 11: *Plasmodium falciparum* malaria. Microscopic examination demonstrates intraerythrocytic parasites with hemozoin in blood vessels of multiple organs; H & E staining, original magnification: ×630. **B)** Traveler 12: Sarcocystosis. Autopsy heart tissue demonstrates numerous *Sarcocystis* species with inflammation and myocyte necrosis; H & E staining, original magnification: ×400. **C–D)** *Balamuthia mandrillaris* granulomatous amebic encephalitis. C) Autopsy brain tissue demonstrates granulomatous inflammation and vascular necrosis with many amebic organisms around the vessel; H & E staining, original magnification: ×400. D)

Immunostaining of many *Balamuthia mandrillaris* in the brain; immunoalkaline phosphate staining, naphthol fast red substrate with light hematoxylin counterstain, original magnification: ×400. **E-F)** Traveler 15: Lassa fever. E) Autopsy liver tissue demonstrates multifocal hepatocellular necrosis, H & E staining, original magnification: ×200. F) Immunostaining of abundant Lassa virus antigens in the liver; immunoalkaline phosphate staining, naphthol fast red substrate with light hematoxylin counterstain, original magnification: ×200. **G–H)** Traveler 18: Rabies. G) Autopsy brain tissue demonstrates meningoencephalitis with viral inclusions (Negri bodies) in cerebellar Purkinje cells; H & E staining, original magnification: ×400. H) Immunostaining of rabies virus antigens in the brain; immunoalkaline phosphate staining, naphthol fast red substrate with light hematoxylin counterstain, original magnification: ×200.

Table 1

International travelers with a biopsy or autopsy specimen submitted to the Centers for Disease Control and Prevention's Infectious Diseases Pathology laboratory, 1995–2015 (n = 21).

Traveler	Year	Age	Sex	Country of Residence	Exposure Country	Travel Reason	Specific Reported Exposures/Behaviors	Clinical Information	Initial Diagnosis	Histopathologic Findings	Organism(s)	Final Diagnosis	Outcome
Travelers with a Biopsy Specimen													
1	2008	45	F	United States	Belize	Unknown	Unknown	Scalp lesion	None	Morphological features compatible with diptera larvae (Fig. 1A)	*Dermatobia hominis*	Myiasis	Unknown
2	2011	62	F	United States	Ghana	Missionary	Questionable exposure to animal hides	Extensive face and arm lesions with ulcerations	Cutaneous anthrax	Diffuse neutrophilic infiltrates in the epidermis and upper dermis with epithelial necrosis (Fig. 1B and C)	Group A *Streptococcus*	Impetigo	Unknown
3	2011	59	M	United States	Panama	Short-term missionary	Constructed a home in a rural area	Myalgia, arthralgia, fever, non-productive cough, dyspnea on exertion, hemoptysis, bilateral patchy infiltrates and mediastinal and hilar lymphadenopathy	None	Necrotizing inflammation with small budding yeasts (Fig. 1D)	*Histoplasma capsulatum*	Acute pulmonary histoplasmosis	Unknown
4	2012	31	M	United States	Papua New Guinea	Unknown	Unknown	Ulcerated and erythematous right thigh lesion, mild pain, fever, swelling of right foot and ankle	Buruli ulcer	Necrotizing dermatitis with hemorrhage, edema, and thrombosis	*Fusobacterium nucleatum* and *Treponema vincentii*	Tropical phagedenic ulcer	Improvement after debridement and cefalexin
5	2014	39	M	United States	Peru	Unknown	Insect bite(s)	Ulcerating lesion on lower leg	None	Lymphohistiocytic infiltrates in dermis with scattered intra- and extracellular round basophilic structures (Fig. 1E and F)	*Leishmania* spp.	New World cutaneous Leishmaniasis	Unknown
6	2015	65	F	United States	South Africa	Unknown	Tick bite(s)	Headache, fever, chills, myalgias	None	Epidermal ulceration and perivascular and periadnexal lymphohistiocytic inflammation (Fig. 1G and H)	*Rickettsia africae*	African tick bite fever (spotted fever rickettsiosis)	Unknown
Travelers with an Autopsy Specimen													
7	1996		M	Romania	South Africa, Gabon, Guinea	Business (ship mate)	Stop in Libreville, Gabon coincided with an Ebola outbreak	Unknown	Ebola	Multiple organs with intraerythrocytic parasites in blood vessels	*Plasmodium falciparum*	Malaria	Death
8	1996		M	Romania	South Africa, Gabon, Guinea	Business (Cargo ship mate)	Stop in Libreville, Gabon coincided with an Ebola outbreak	Unknown	Ebola	Multiple organs with intraerythrocytic parasites in blood vessels	*Plasmodium falciparum*	Malaria	Death
9	2004	36	M	United States	Nigeria, Sierra Leone, Côte d' Ivoire	Business (Second mate on cargo ship)	Port calls in Freetown, Sierra Leone; Abidjan, Côte d'Ivoire; Lagos, Nigeria; unknown malaria chemoprophylaxis	Fever, chills, headache, myalgias, sore throat, nausea, vomiting, jaundice, abdominal pain, bloody urine	Lassa fever	Multiple organs with extensive intraerythrocytic parasites in blood vessels	*Plasmodium falciparum*	Malaria	Death
10	2005	43	M	United States	Central African Republic, Côte d'Ivoire	Missionary	Did not take malaria chemoprophylaxis	Fever, cough, myalgias, arthralgias, "dark urine"	Yellow fever, Dengue	Multiple organs with intraerythrocytic parasites in blood vessels	*Plasmodium falciparum*	Malaria	Death
11	2011	4	F	United States	Uganda	Visiting friends and relatives	Did not take malaria chemoprophylaxis	Fever, cough, diarrhea, vomiting	Bacterial infection	Multiple organs with extensive intraerythrocytic parasites in blood vessels (Fig. 2A)	*Plasmodium falciparum*	Malaria	Death
12	2010	30	F	Sudan	Sudan or Kenya	Refugee	Unknown	Heart failure	None	Myocarditis with protozoal organisms (Fig. 2B)	*Sarcocystis* spp.	Sarcocystosis	Death
13	2011	2	M	United States	Mexico	Unknown	Swam in a hotel pool	Cough, rhinorrhea, left hemiparesis	Neurocysticercosis	Granulomas with amebic organisms (Fig. 2C and D)	*Balamuthia mandrillaris*	Granulomatous amebic encephalitis	Death
14	1999	45	M	United States	Venezuela	Tourism	Ten days in rainforest, swam in ponds and rivers	Renal and liver failure, disseminated intravascular coagulation, intracerebral hemorrhage	None	Massive hepatocellular necrosis	Yellow fever virus	Yellow fever	Death
15	2004	38	M	United States	Liberia or Sierra Leone	Business	Visited farms in Sierra Leone	Fever, chills, sore throat, diarrhea, back pain, acute respiratory distress syndrome	Malaria, typhoid fever	Multifocal hepatocellular necrosis (Fig. 2E and F)	Lassa virus	Lassa fever	Death

Traveler	Year	Age	Sex	Country of Residence	Exposure Country	Travel Reason	Specific Reported Exposures/Behaviors	Clinical Information	Initial Diagnosis	Histopathologic Findings	Organism(s)	Final Diagnosis	Outcome
16	2008	33	M	Zambia	Airplane to South Africa	Business	Mechanically ventilated an ill woman on a medical evacuation flight	Headache, myalgia, fever	None	Scattered hepatocellular necrosis	Lujo virus	Old World arenavirus, viral hemorrhagic fever	Death
17	2010	12	F	United States	Philippines	Visiting friends and relatives	Swam	Headache, fever, nausea, vomiting, seizures, altered mental status	Bacterial meningitis	Meningoencephalitis with neuronal necrosis, neuronophagia, and glial nodules	Japanese encephalitis virus	Japanese Encephalitis	Death
18	2011	24	M	United States	Afghanistan	Military	Bitten by a dog on the right hand	Severe arm pain and right hand paresthesias, difficulty swallowing, vomiting, ataxia	Tendonitis, Gastritis	Meningoencephalitis with viral inclusions in Purkinje cells (Fig. 2G and H)	Rabies virus	Rabies	Death
19	2011	73	F	Haiti	Haiti	Visiting friends and relatives	Bitten by a dog	Right shoulder pain, headaches, difficulty swallowing, shortness of breath, muscle spasms, hallucinations, difficulty maintaining balance	None	Meningoencephalitis with viral inclusions in Purkinje cells	Rabies virus	Rabies	Death
20	1995	38	F	Switzerland	Burundi	Business	Cared for ill prison inmates with unexplained deaths	High fever, chills, myalgias, severe thrombocytopenia	Viral hemorrhagic fever, typhoid fever	Vasculitis in multiple organs	*Rickettsia prowazekii*	Epidemic (louse-borne) typhus	Death
21	1999	39	F	United States	Kenya	Missionary	Lived in a rural area, hiked in the forest with her dog, who had “tick-borne fever” prior to her illness	Left leg eschar, fever, chills, myalgias, macular rash sparing the palms and soles, abdominal pain, vomiting	Malaria	Vasculitis and microthrombi in multiple organs	Unknown	Spotted Fever Rickettsiosis	Death