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Adrenal gland hemorrhage in patients with fatal bacterial infections

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A wide spectrum of adrenal gland pathology is seen during bacterial infections. Hemorrhage is particularly associated with meningococcemia, while abscesses have been described with several neonatal infections. We studied adrenal gland histopathology of 65 patients with bacterial infections documented in a variety of tissues by using immunohistochemistry. The infections diagnosed included *Neisseria meningitidies*, group A streptococcus, *Rickettsia rickettsii*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Ehrlichia* sp., *Bacillus anthracis*, *Leptospira* sp., *Clostridium* sp., *Klebsiella* sp., *Legionella* sp., *Yersinia pestis*, and *Treponema pallidum*. Bacteria were detected in the adrenal of 40 (61%) cases. Adrenal hemorrhage was present in 39 (60%) cases. Bacteria or bacterial antigens were observed in 31 (79%) of the cases with adrenal hemorrhage including 14 with *N. meningitidis*, four with *R. rickettsii*, four with *S. pneumoniae*, three with group A streptococcus, two with *S. aureus*, two with *B. anthracis*, one with *T. pallidum*, and one with *Legionella* sp. Bacterial antigens were observed in nine of 26 non-hemorrhagic adrenal glands that showed inflammatory foci (four cases), edema (two cases), congestion (two cases), or necrosis (one case). Hemorrhage is the most frequent adrenal gland pathology observed in fatal bacterial infections. Bacteria and bacterial antigens are frequently seen in adrenal glands with hemorrhage and may play a pathogenic role. Although *N. meningitidis* is the most frequent bacteria associated with adrenal gland pathology, a broad collection of bacteria can also cause adrenal lesions.
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A wide spectrum of adrenal gland pathology is seen during bacterial infections including massive hemorrhage, abscesses, and granulomas. Adrenal hemorrhage is an uncommon condition associated to a variety of infectious and non-infectious diseases. The non-infectious conditions that can cause adrenal hemorrhage include postoperative state, thromboembolic diseases, anticoagulant treatment, burns, trauma, tumor metastasis, and cardiovascular catastrophes.[1] *N. meningitidis* is the most frequent infection associated with adrenal hemorrhage; however, *Haemophilus influenzae, Streptococcus pneumoniae, Staphylococcus aureus*, group A streptococcus, *Neisseria gonorrheae, Pseudomonas aeruginosa*, and *Klebsiella oxytoca* are among other bacteria associated with this pathology.[2–10] Endotoxin-mediated septic shock is the most frequent clinical condition seen in patients with infectious adrenal hemorrhage. These endotoxins, lypopolysaccharide in the case of Gram-negative bacteria and peptidoglycan for Gram-positive bacteria, bind through toll-like receptors to endothelial and inflammatory cells and induce a number of signaling pathways that lead to transcription of coagulation, fibrinolysis, and proinflammatory cytokine genes such as tissue factor, IL-1, IL-6 and TNFα.[11] In experimental animal models, hemorrhagic adrenal necrosis can be caused by intravenous injection of bacterial endotoxin after pretreatment with adrenocorticotropic hormone.[12] Although correlation between adrenal hemorrhage and presence of bacteria in the gland has not been described, one report detected *N. meningitides* and *H. influenzae* in six of 11 (55%) adrenal glands of patients with septicemia by using immunofluorescent techniques.[13]

We studied formalin-fixed, paraffin-embedded adrenal glands from cases that were found to have immunohistochemical evidence of a bacterial infection in a variety of tissues in an effort to define the frequency of presence of microorganisms in adrenal glands of patients with fatal bacterial infections and

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the possible role played by bacteria and bacterial antigens in the pathogenesis of adrenal pathology.

Materials and methods

During 1998–2006, the Centers for Disease Control and Prevention (Atlanta, GA) received 65 consultation cases that were found to have immunohistochemical evidence of a bacterial infection in different tissues and adrenal glands were included in the tissue submitted for diagnostic evaluation. Testing performed in these cases was carried out as a component of public health response. Tissues sent for study and demographic and clinical data varied in completeness from case to case.

Using hematoxylin and eosin stains, adrenal glands were evaluated for the presence of hemorrhage (defined as erythrocytes outside sinusoids), inflammation, edema, and cell necrosis. The amount of hemorrhage and inflammation was assessed as focal when it did not extend beyond a $\times 20$ field and extensive if it was greater than a $\times 20$ field. Kidneys were evaluated for the presence of thrombi and hemorrhage and lungs were evaluated for the presence of hemorrhage and pneumonia. Presence of bacteria was determined by using Brown and Brenn Gram and Steiner silver impregnation stains, and immunohistochemical assays. Immunohistochemical assays for infectious agents have been previously validated and described (Table 1).[14–24] In summary, assays were performed on deparaffinized, rehydrated 3-μm tissue sections. Proteinase K (Roche, Indianapolis, IN, USA) digestion was carried out for slides treated with all antibodies except for those treated with the anti-*Clostridium* spp. antibody. Incubation with a primary antibody (Table 1) and colorimetric detection with the LSAB2 Universal alkaline phosphatase kit (Dako, Carpinteria, CA, USA) were performed in the autostainer (Dako). Sections were counterstained with Mayer's hematoxylin (Fisher Scientific, Pittsburgh, PA, USA). Interpretation of immunohistochemical results included the location of the positive reaction and the staining pattern (cocci, bacilli, and granular antigen staining). Systemic disease was defined when immunohistochemical staining was present outside the primary focus of infection. If immunohistochemical staining was only present in the focus of infection it was considered localized, for example, pneumonia.

All primary antibodies were prepared at the Centers for Disease Control and Prevention, except for the antibodies against *S. aureus* (Biodesign, Saco, ME, USA), *N. meningitidis* (Center for Biologics Evaluation and Research, Food and Drug Administration), *Clostridium* spp (Biodesign) and *K. pneumoniae* (Biogenesis, Kingston, NH, USA). Positive controls for the primary antibodies included formalin-fixed, paraffin-embedded bacteria and cases with known bacterial and viral infections (Table 1). Negative controls consisted of sequential case–patient tissue sections incubated with normal rabbit, dog, or horse serum as the primary antibody.

Results

Table 2 presents the frequency of infectious agents diagnosed in these 65 patients, their demographic data, the frequency of systemic disease for each microorganism or the syndrome when localized disease was present, and pathological data relating to hemorrhage or thrombosis. None of the cases had an adrenal adenoma. Systemic disease was present in 54 (83%) of 65 cases. Five (28%) of the 18 patients with meningococcemia had meningitis. Seven (78%) of the nine patients with group A streptococcus septicemia had a primary focus of infection including five with a respiratory focus (tonsillitis, laryngeal abscess, or pneumonia), one with necrotizing endometritis, and one with necrotizing fasciitis. The syndromes of the 11 patients with localized disease included pneumonia caused by *S. pneumoniae* (four cases), *S. aureus* (2), or *K. pneumoniae* (1), necrotizing endometritis caused by *Clostridium sordellii* (2), mediastinal hemorrhage caused by *B. anthracis* (1), and necrotizing fasciitis due to group A streptococci (1).

Pathologic evidence of adrenal hemorrhage was found in 39 (60%) of 65 cases, all having systemic disease except for two cases (one with pneumonia the other with necrotizing fasciitis). Glomerular thrombi were observed in 13 (29%) of 45 kidneys studied and lung hemorrhages in 10 (23%) of 44 lung specimens available. The frequency of glomerular thrombi and lung hemorrhage by organism is presented in Table 2; of note glomerular thrombi were observed in 50% of the cases with *N. meningitidis* and group A streptococci while 66% of the cases with *B. anthracis* had lung hemorrhage. Fourteen (36%) of 39 cases with adrenal hemorrhage had glomerular thrombi and hemorrhages in other organs, including seven (18%) with glomerular thrombi, four (10%) with lung hemorrhages, two (5%) with kidney hemorrhages, and one with both glomerular thrombi and lung hemorrhages.

Steiner silver impregnation stains showed bacteria (Figure 1a) in nine (15%) of the 60 adrenal blocks available. In the remaining 51 blocks formalin pigment, neurosecretory granules, and reticulin made definitive diagnosis of bacteria very difficult. Bacteria were detected with the Gram stain in 14 (23%) of 60 cases in which adrenal blocks were available. Gram-positive cocci (Figure 1b) were identified in 10 cases, Gram-negative cocci (Figure 1c) in three, and a mixed population of Gram-positive and -negative cocci and bacilli were detected in one case. By using immunohistochemistry, bacteria and bacterial antigens were detected in 40 (61%) of 65 adrenal glands.

Table 1 Antibodies used in immunohistochemical assays

Antibody against	*Animal source*	*Dilution*	*References*
Neisseria meningitidis[a]	Horse	1:500	[14]
Group A streptococcus[b]	Rabbit	1:2000	[15]
Rickettsia rickettsii[c]	Rabbit	1:500	[16]
Streptococcus pneumoniae[d]	Rabbit	1:3000	[17]
Staphylococcus aureus[e]	Rabbit	1:500	[18]
Ehrlichia spp.[f]	Dog	1:100	[19]
Bacillus anthracis cell wall	Mouse	1:200	[20]
Leptospira spp.[g]	Rabbit	1:400	[21]
Clostridium spp.[h]	Rabbit	1:1000	[18]
Klebsiella pneumoniae[i]	Rabbit	1:200	
Legionella pneumophila	Rabbit	1:10 000	[22]
Yersinia pestis	Rabbit	1:3000	[23]
Treponema pallidum	Rabbit	1:200	[24]

[a]The *N. meningitidis* antibody does not react with group A streptococcus (GAS), *S. aureus*, Listeria monocytogenes, *B. anthracis*, *Francisella tularensis*, *Haemophilus influenzae*, *Mycoplasma pneumoniae, Pseudomonas spp., or R. rickettsii*.

[b]The GAS antibody does not react with *S. pneumoniae*, group B streptococcus (GBS), *S. aureus, B. anthracis, Clostridium spp, L. monocytogenes, H. influenzae, Mycobacterium tuberculosis, N. meningitidis, or R. rickettsii*.

[c]Th *Rickettsia spp*. antibody will cross-react with various spotted fever group rickettsiae, including *R. rickettsii, R. akari, R. parkeri, R. africae, and R. conorii*.

[d]The *S. pneumoniae* antibody does not react with GAS, GBS, *S. aureus*, *B. anthracis, F. tularensis, L. pneumophila, Leptospira spp., H. influenzae, K. pneumoniae, M. pneumoniae, M. tuberculosis, N. meningitidis, or Y. pestis*.

[e]The *S. aureus* antibody does not react with GAS, GBS, *S. pneumoniae*, *B. anthracis, Clostridium spp., K. pneumoniae, Pseudomonas spp., or N. meningitidis*.

[f]The *Ehrlichia spp*. antibody cross-reacts with *E. canis, E. chaffeensis* and *E. ewingii*.

[g]The *Leptospira* antibody is a mixture of 16 reference rabbit polyclonal anti-leptospira antisera.

[h]The *Clostridium* antibody reacts with various clostridia, including *C. perfringens, C. botulinum, C. sordelii, C. novyii, and C. subterminale*.

[i]The *K. pneumoniae* antibody does not react with GAS, GBS, *S. pneumoniae, B. anthracis*, *Clostridium spp., F. tularensis, H. influenzae, L. pneumophila, Leptospira spp., N. meningitidis, M. pneumoniae, or R. rickettsii*.

Various amounts of bacteria and bacterial antigens were present at the site of the hemorrhage in 31 (79%) of 39 cases with adrenal hemorrhage. Hemorrhage was considered extensive (Figure 2a) in 19 cases and focal in the other 20. Of those patients with extensive hemorrhage 15 (79%) had bacteria and bacterial antigens while for those with focal hemorrhage 16 (80%) had bacteria and bacterial antigens. The amount of bacteria and bacterial antigens did not correlate with the amount of hemorrhage. Adrenal hemorrhage not associated with bacterial antigens was observed in eight (12%) cases. *N. meningitidis* antigens were observed in 14 (36%) adrenals with hemorrhage (Figure 2b), other bacterial antigens present in adrenals with hemorrhage included group A streptococcus (three cases), *S. pneumoniae* (4), *R. rickettsii* (4), *S. aureus* (2), *B. anthracis* (2), *T. pallidum* (1), and *L. pneumophila* (1). In addition to hemorrhage, seven adrenals showed small foci of inflammation all associated with bacteria and bacterial antigens and included four cases with *R. rickettsii* and one of each *N. meningitidis, S. aureus,* and *S. pneumoniae*. In the cases with rickettsial infections the inflammation and bacterial antigens were primarily localized in blood vessels of the capsule and sparsely in cortical sinusoids.

Adrenal glands without hemorrhage were present in 26 (40%) cases and were associated with bacteria and bacterial antigens in nine. In these nine adrenals the bacteria and bacterial antigens were associated with various pathologic lesions including small inflammatory foci in four patients (two with *Ehrlichia* spp. (Figure 2c), one with *R. rickettsii* (Figure 2d), and one with *Leptospira* spp.), foci of necrosis in one (with *Leptospira* spp.), and in areas of edema and congestion in the remainder four (two with group A streptococci, one with *R. rickettsii* and one with *Y. pestis*). Seventeen adrenals showed no evidence of bacteria and no hemorrhage including *N. meningitidis* (two cases), group A streptococci (2), *S. pneumoniae* (4), *R. rickettsii* (3), *S. aureus* (2), *B. anthracis* (1), *Clostridium* spp. (2), and *K. pneumoniae* (1). Only three of the 17 adrenal glands without hemorrhage and no evidence of bacteria or bacterial antigens showed significant pathology including a *R. rickettsii* case that had inflammatory foci and two cases with *S. aureus* septicemia that showed necrotic foci in the adrenal gland.

Of the 25 patients without bacteria in the adrenal glands, 14 had systemic disease. The cases with systemic disease but without bacteria in the adrenal glands included four cases with meningococcemia (three of them with meningitis), three cases with pneumonia due to group A streptococci, three with Rocky Mountain spotted fever, two with *S. aureus* pneumonia, one with meningitis caused by *S. pneumoniae*, and one with *Ehrlichia* spp.

Table 2 Number of cases with each infection, demographic data, syndromic information and pathological findings

Infectious agent	*No. of cases*	*Mean age (range)*	*No. of males*	*No. with systemic disease/ no. with antigens in adrenals*	*No. without systemic disease (syndrome)*	*Adrenal hemorrhage*	*Glomerular thrombi*	*Lung hemorrhage*
Neisseria meningitidis	18	14 (1–52)	9	18/14	0	16 (89%)	6/12	1/12
Group A streptococcus	9	23 (0.5–59)	6	8/5	1 (necrotizing fasciitis)	5 (56%)	2/4	0/3
Streptococcus pneumoniae	9	21(1–53)	7	5/4	4 (pneumonia)	5 (56%)	1/7	0/7
Rickettsia rickettsii	9	19 (1–54)	6	9/6	0	4 (44%)	1/7	2/6
Staphylococcus aureus	6	28 (5–44)	3	4/2	2 (pneumonia)	4 (67%)	1/6	2/6
Bacillus anthracis	3	69 (49–94)	2	2/2	1 (mediastinal hemorrhage)	2 (67%)	1/3	2/3
Ehrlichia sp.	3	42 (22–66)	3	3/2	0	1 (33%)	0/1	1/1
Leptospira sp.	2	28 (16–40)	1	2/2	0	0	0/1	1/1
Clostridium sp.	2	19 (18–20)	0	0	2 (necrotizing endometritis)	0	0/2	1/2
Yersinia pestis	1	13	1	1/1	0	0	1/1	0/1
Klebsiella pneumoniae	1	6 months	1	0	1 (pneumonia)	0	0	0/1
Treponema pallidium	1	Fetus	0	1/1	0	1	0	0
Legionella pneumophila	1	44	1	1/1	0	1	0/1	0/1

Discussion

Hemorrhage was the most frequent adrenal gland pathology observed in this series of fatal bacterial infections. In our series, bacteria and bacterial antigens were seen in almost 80% of the adrenal glands with hemorrhage; however, the exact pathogenic role they play in the development of this pathology is not clear, as there are cases with adrenal gland hemorrhage without demonstrable bacteria. Adrenal hemorrhage usually occurs in the setting of a life-threatening illness, such as sepsis, in which there are low cortisol levels and consequently increased adrenocorticotropic hormone.[1,25] In experimental animal models, it is necessary to have an adrenocorticotropic hormone-stimulated gland that is challenged by endotoxin or another condition such as hypovolemia to create adrenal hemorrhage.[12,26] Consequently, presence of detectable bacteria in the gland is not considered essential for the occurrence of adrenal hemorrhage. In our series, the amounts of bacteria and bacterial antigens varied from patient to patient and did not correlate with the extent of hemorrhage; hence, it is possible that bacteria could have been present in areas that were not tested in those cases with hemorrhage but no bacteria in the adrenal glands. Our data suggest that the presence of bacteria in the gland may only be a consequence of the septicemia.

In a series of 22 cases with bilateral adrenal hemorrhage that included infectious and non-infectious etiologies, 59% of cases showed hemorrhages into other organs which were attributed to coagulation abnormalities including use of anticoagulants.[1] It is estimated that 21% of cases with septicemia have laboratory evidence of disseminated intravascular coagulation.[27] We searched for pathologic evidence of glomerular thrombi (hypercoagulable stage) and lung hemorrhage (fibrinolytic stage) in our cases. The proportion of cases in our series with thrombi or hemorrhage in other organs and adrenal hemorrhage was 36%, which is higher than the frequency of disseminated intravascular coagulation in cases with septicemia. The higher frequency of lung hemorrhage in our series could be accounted for by specific pathogenetic bacterial mechanisms, that is, rickettsiae and leptospira damage vessel walls causing hemorrhages in various organs.

Although meningococci are the bacteria most commonly associated with adrenal hemorrhage, a broad collection of bacteria can cause it. In our series, *N. meningitidis* was the most frequently associated bacteria, followed by group A streptococci, *S. pneumoniae*, *R. rickettsii*, and *S. aureus*. Of the bacteria mentioned *N. meningitides,* group A streptococci, *S. pneumoniae* and *S. aureus* can circulate systemically in blood vessels and enter sinusoidal spaces of multiple organs including the adrenal gland and cause disseminated intravascular coagulation due to endotoxin production.[2,3,5,6] On the other hand, rickettsiae infect endothelial cells and can cause blood vessel leakage with consequent hemorrhages in various organs.[28] Independent of their pathogenic mechanism, clinical manifestations of Rocky Mountain spotted fever are similar to meningococcemia, including skin rash which together with adrenal hemorrhage is part of Waterhouse-Friderichsen syndrome. It is interesting that bacteria that have different pathogenic mechanisms can cause similar pathology: adrenal hemorrhage.

In our series, 40% of the adrenal glands did not show hemorrhage and a variety of pathologic features were observed especially if the bacteria were present in the gland. Inflammation in the area where the bacteria were located was the most frequent lesion; however, formation of small abscesses was not encountered in this series. *Escherichia coli, S. aureus*,

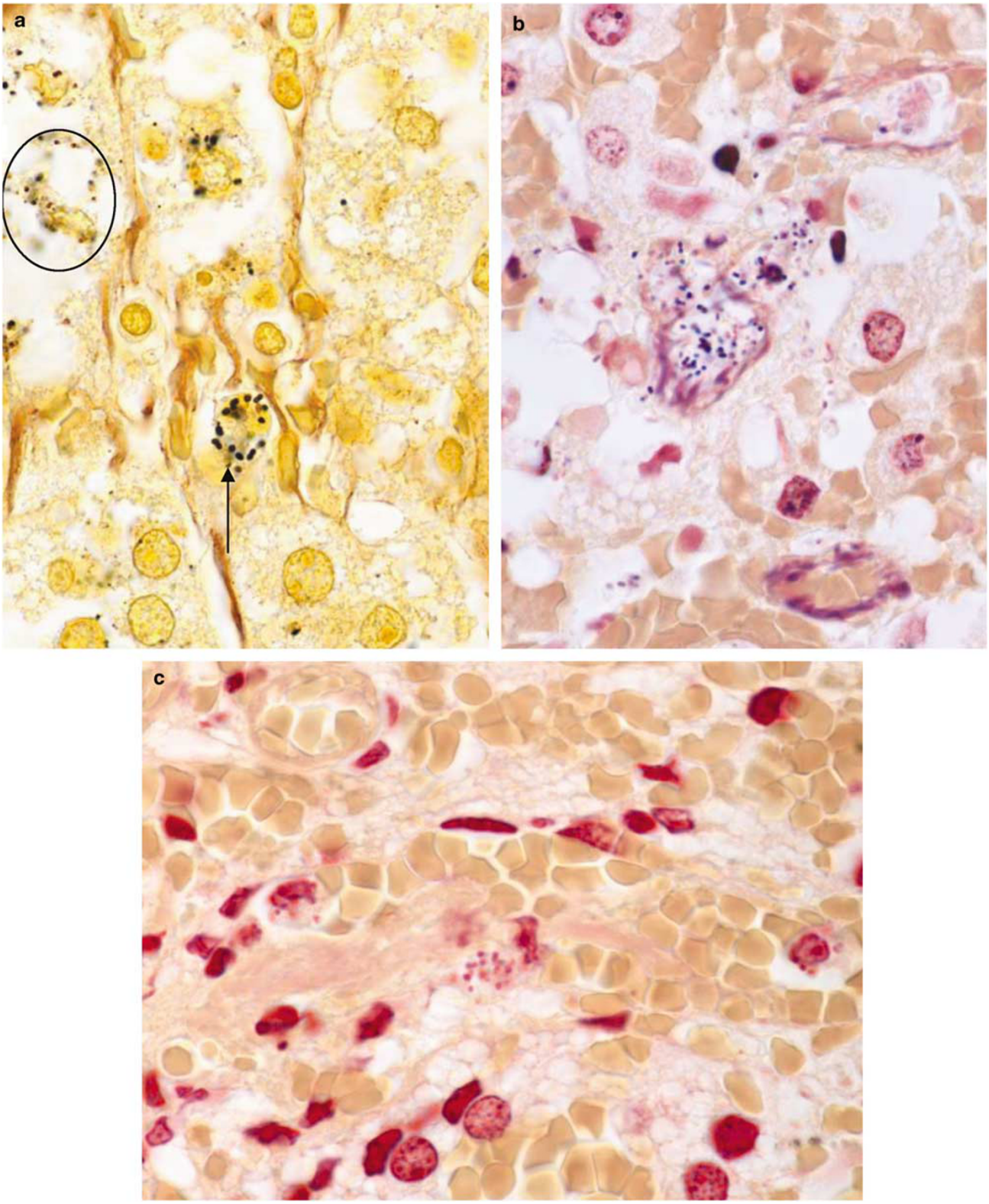

Figure 1 Special stains for bacteria including Steiner silver impregnation stain (**a**) showing diplococci (arrow) in a patient with invasive pneumococcal disease. Note that neurosecretory granules (circle) can make diagnosis of the bacteria difficult with silver staining techniques. Gram's stains demonstrating Gram-positive (**b**) and Gram-negative (**c**) cocci in adrenal glands of patients with invasive pneumococcal disease and meningococcemia respectively (Original magnification for (**a**, **b**, and **c** $\times 250$).

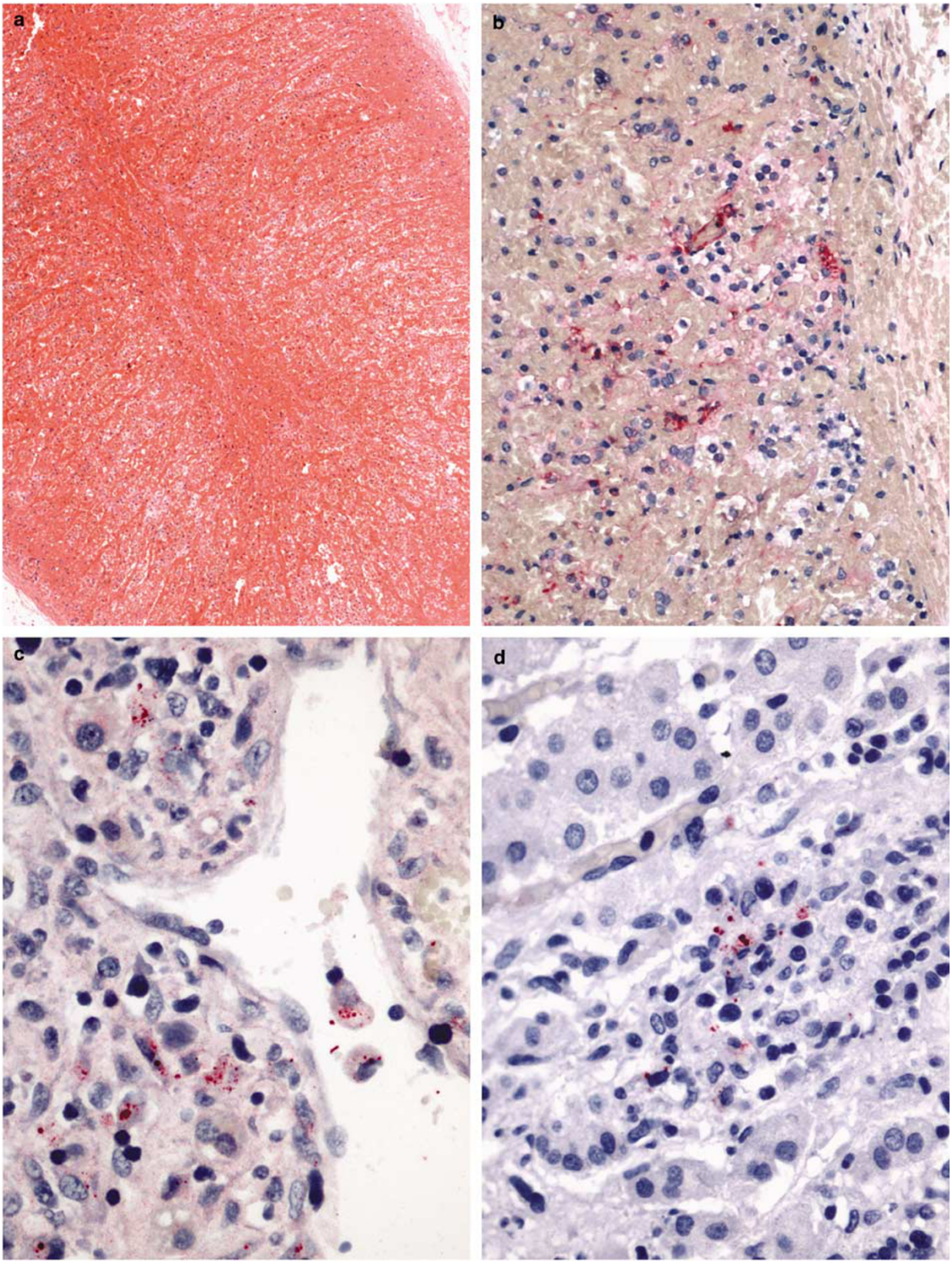

Figure 2 Extensive adrenal hemorrhage and necrosis present in a patient with meningococcemia (**a**). Immunohistochemical assay showing meningococci (**b**) in a patient with adrenal hemorrhage, *Ehrlichia* spp. (**c**) and *Rickettsia rickettsii* (**d**) in adrenals showing inflammatory foci. (**a**): hematoxylin and eosin stain; (**b**, **c**, and **d**): immunohistochemical assays where primary antibodies were detected with naphthol fast red; original magnification (**a**) 12.5, (**b**) 50, (**c** and **d**) $\times 100$.

and *Candida albicans* have been reported to cause adrenal gland abscesses in neonates whereas granulomas have been described in cases with *Mycobacterium tuberculosis*.[29–31] In our series, the organisms found in the adrenal gland associated with inflammation included *R. rickettsii*, and *Leptospira* spp., infections that are characterized by inflammatory changes around blood vessels.[16,22,28] The other organism associated with inflammatory foci in the adrenal was *Ehrlichia* spp. The now known *Anaplasma phagocytophilum* have not been previously detected in human adrenal glands of patients with granulocytic ehrlichiosis; however, they have been observed in adrenal glands of experimentally infected horses.[32]

The cases in our series were selected because there was an immunohistochemical diagnosis of bacterial infection. Undoubtedly, our series shows a bias because the Centers for Disease Control and Prevention receives cases of public health importance that need to be reported such as meningococcemia and those that are difficult to diagnose with routine histopathologic methods such as *R. rickettsii*, *Ehrlichia* spp., and *Leptospira* spp. In this series, *H. influenzae* infection was not diagnosed even though it has been associated with adrenal hemorrhage.[8,10]

Immunohistochemical assays permitted identification of intact bacteria (bacilli and cocci) and granular antigen staining. Detection of bacterial antigens using immunohistochemical assays has been observed in various bacterial infections including those caused by *N. meningitidis*, *Clostridium* spp., *B. anthracis*, *Leptospira* spp., and *T. pallidum*.[14,18,20,22,24] In some of these infections, particularly if antibiotic therapy has been given, bacterial antigens can be more abundant than intact bacteria and in some cases antigens can be the only evidence of the causative infectious agent. These antigens probably represent break down products of the bacteria including endotoxins, which may be important contributors to adrenal hemorrhage.

This study expands on others that document adrenal hemorrhage in bacterial infections. It shows that a broad collection of bacteria can cause adrenal hemorrhage in addition to the classically associated meningococci. Immunohistochemistry allowed detection of bacterial antigens in adrenal glands with hemorrhage and may be useful to further define the pathogenic role of bacteria in this entity. Immunohistochemical assays can be of great diagnostic value, particularly for bacteria such as *R. rickettsii, Ehrlichia* spp*., Leptospira* spp., and *Clostridium* spp., which are difficult to isolate.

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