7
Endometritis

Endometritis usually is a disorder of the reproductive years, although it may occur in postmenopausal patients. Endometrial inflammation typically accompanies pelvic inflammatory disease of the upper genital tract.[1;2] It may also be associated with a recent pregnancy, either an abortion or a term pregnancy.[3–5] Other possible causes include instrumentation, such as a prior biopsy, an intrauterine contraceptive device, cervical stenosis, or the presence of an organic lesion such as a polyp, leiomyoma, hyperplasia, or carcinoma.[5] Endometritis typically presents with intermenstrual vaginal bleeding, and sometimes it causes menorrhagia. This disorder also may be associated with infertility,[6;7] although some studies find no association between endometritis and decreased fertility.[8] In one study, 8% of outpatient endometrial biopsies, most of which were done for abnormal bleeding, showed chronic endometritis.[9] In our experience, endometritis is an infrequent diagnosis, however, and the prevalence of this disorder appears to vary greatly depending on the practice setting.

Endometrial inflammation often is nonspecific and rarely has morphologic features that indicate a definite etiology. The nonspecific forms of endometritis traditionally have been separated into chronic and acute forms, depending on the type of inflammatory infiltrate; most are referred to as chronic nonspecific endometritis. The inflammatory infiltrate often is a mixed acute and chronic inflammatory process, however, and neutrophils as well as plasma cells and lymphocytes can be present. Rigorous separation of the type of inflammatory process is less important than recognition of the presence of inflammation. Acute endometrial inflammation is relatively infrequent except for puerperal-related infections, and these latter cases rarely come to biopsy or curettage.

Nonspecific Endometritis

Endometritis may be diffuse or focal and can range from a subtle inflammatory infiltrate to a pronounced inflammatory reaction. Endometritis typically shows a pattern of a mixed inflammatory infiltrate containing plasma cells and lymphocytes, and, not infrequently, neutrophils (polymorphonuclear leukocytes) and eosinophils. In addition to inflammatory cells, there is a constellation of

TABLE 7.1. Morphologic features of nonspecific endometritis.

Plasma cell infiltrate
Increased number of lymphocytes and lymphoid follicles
Variable presence of neutrophils in surface epithelium and glands
Reactive stromal response
Altered gland development
Breakdown and bleeding

histologic findings that facilitate recognition of endometrial inflammation (Table 7.1).[9] The other morphologic changes include reactive stroma, epithelial changes, abnormal glandular development, and evidence of glandular and stromal breakdown.[9;10]

Inflammatory Cells

Plasma cells are the most important histologic feature for the diagnosis of endometritis.[4;5;11;12] Their presence is required to establish the diagnosis of chronic endometritis, because, in contrast to lymphocytes, they are not present in normal endometrium. Plasma cells may be diffuse and easily recognizable but more commonly are focal and widely dispersed. Plasma cells generally are most numerous in the periglandular and subepithelial stroma and around lymphoid aggregates (Fig. 7.1). Plasma cells should be readily identifiable and numerous before a diagnosis of chronic endometritis is established unless associated features of inflammation are clearly present (see later).[9] The diagnosis of endometritis should not rest on the finding of an apparent plasma cell, however, in endometrium that otherwise appears normal. In cases in which the plasma cell infiltrate appears subtle or equivocal, the background pattern is as important as the quantity of plasma cells for establishing the diagnosis of endometritis. The number of plasma cells does not appear to correlate with the severity of the lesion.[3;9]

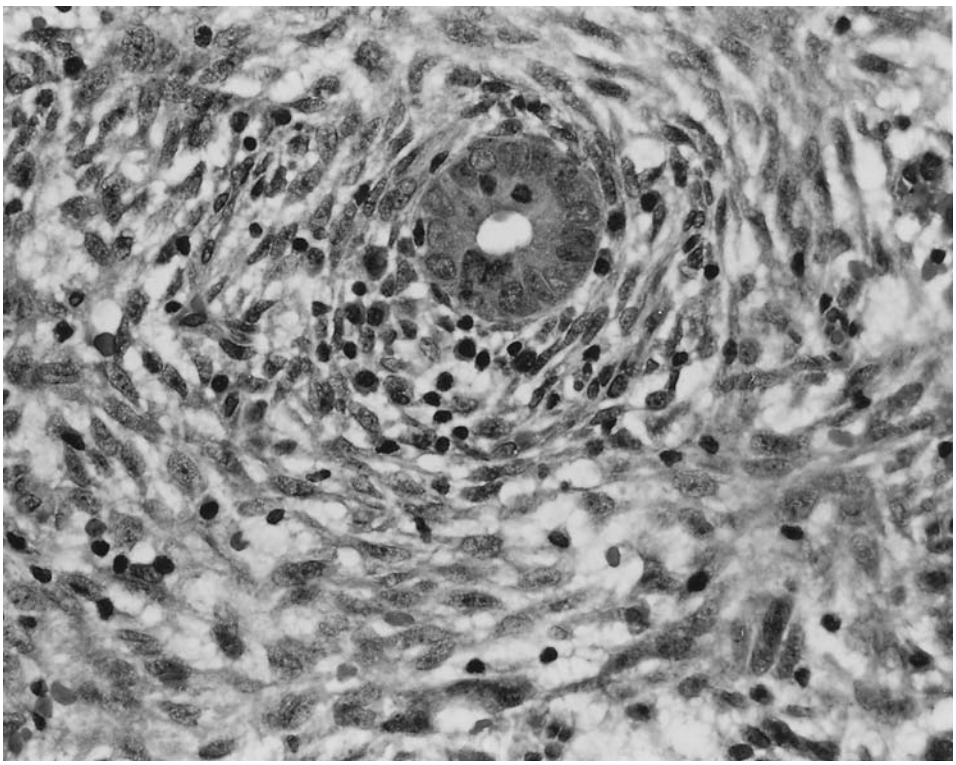

FIGURE 7.1. Nonspecific chronic endometritis. Scattered plasma cells and lymphocytes surround a small proliferative gland. The stromal cells are reactive, with elongated, spindle-shaped nuclei, and they swirl around the gland.

Normal endometrial stromal cells, especially predecidualized cells in the late secretory phase, can resemble plasma cells, having eccentric nuclei and a pale perinuclear zone. The plasma cell, however, is identified by its distinctive, clumped chromatin arrangement yielding a clock-face pattern. A methyl green pyronin histochemical stain,[4] immunohistochemistry for immunoglobulin G[13] or syndecan,[14] and in situ hybridization for kappa and lambda immunoglobulin light chains[15] can help demonstrate plasma cells when the cytologic features are not diagnostic by routine histology.

Whereas plasma cells may be the predominant inflammatory component of endometritis, more severe inflammation commonly shows a mixed inflammatory infiltrate. Often the inflammatory infiltrate includes numerous lymphocytes that tend to concentrate in the subepithelial stroma (Fig. 7.2). Lymphoid follicles become prominent (Fig. 7.3) and may show germinal centers; larger transformed lymphocytes and immunoblasts also may be interspersed (Fig. 7.4).[16–18]

Neutrophils as a part of the inflammatory infiltrate indicate an acute process (Figs. 7.2 and 7.5). This neutrophilic inflammatory infiltrate typically infiltrates the surface epithelium and extends into gland lumen, sometimes forming microabscesses in the glands.[9–12] Neutrophils, however, also can be present in menstrual endometrium, where foci of glandular and stromal breakdown are present, too, without signifying an infectious process. Therefore, like the presence of lymphocytes, the presence of neutrophils alone is not sufficient to indicate inflammation. The pattern of distribution of these cells in the endometrium and the accompanying cellular infiltrate, usually including

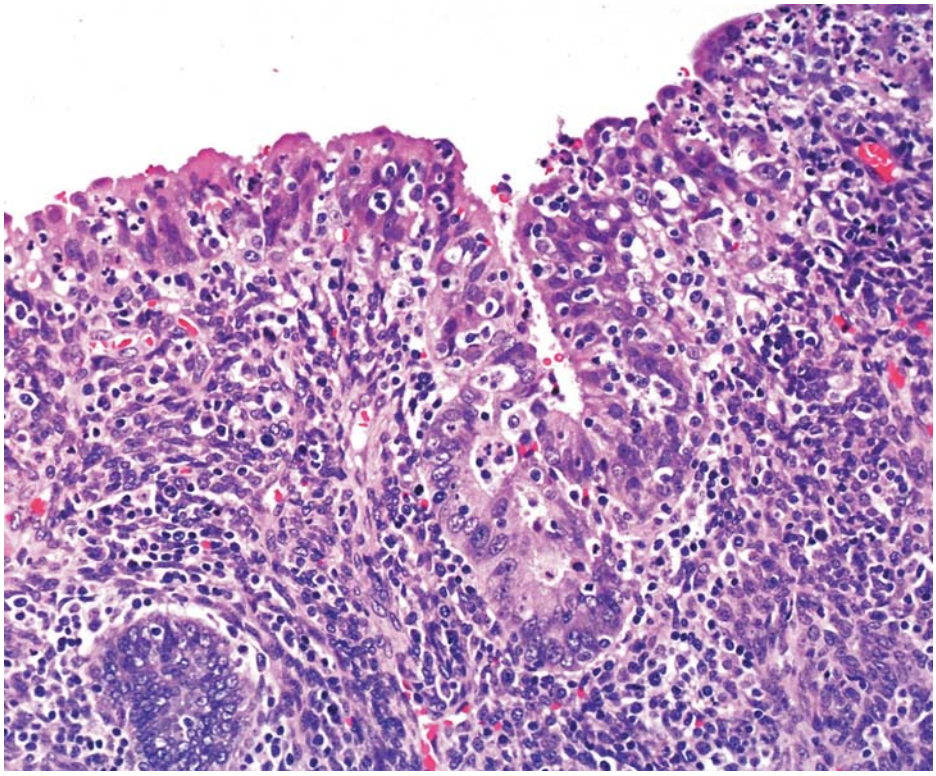

FIGURE 7.2. Nonspecific acute and chronic endometritis. A dense inflammatory infiltrate composed of plasma cells and lymphocytes is present in the stroma. A few neutrophils and lymphocytes infiltrate the subepithelial stroma and extend into the surface epithelium. The stroma has a reactive pattern, with spindle-shaped cells.

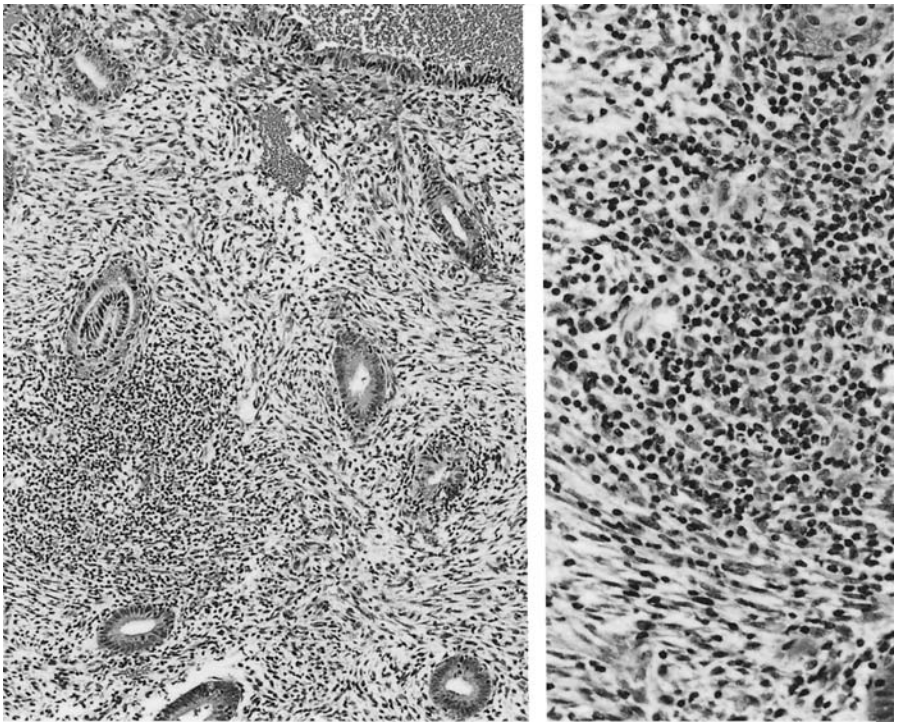

FIGURE 7.3. Nonspecific chronic endometritis. *Left*: Proliferative glands surrounded by spindle-shaped stromal cells. A lymphoid follicle is present. *Right*: The lymphoid follicle is composed predominantly of lymphocytes, but scattered plasma cells also are present. The presence of plasma cells distinguishes inflammatory lymphoid follicles from normal lymphoid follicles that occur in noninflamed endometrium.

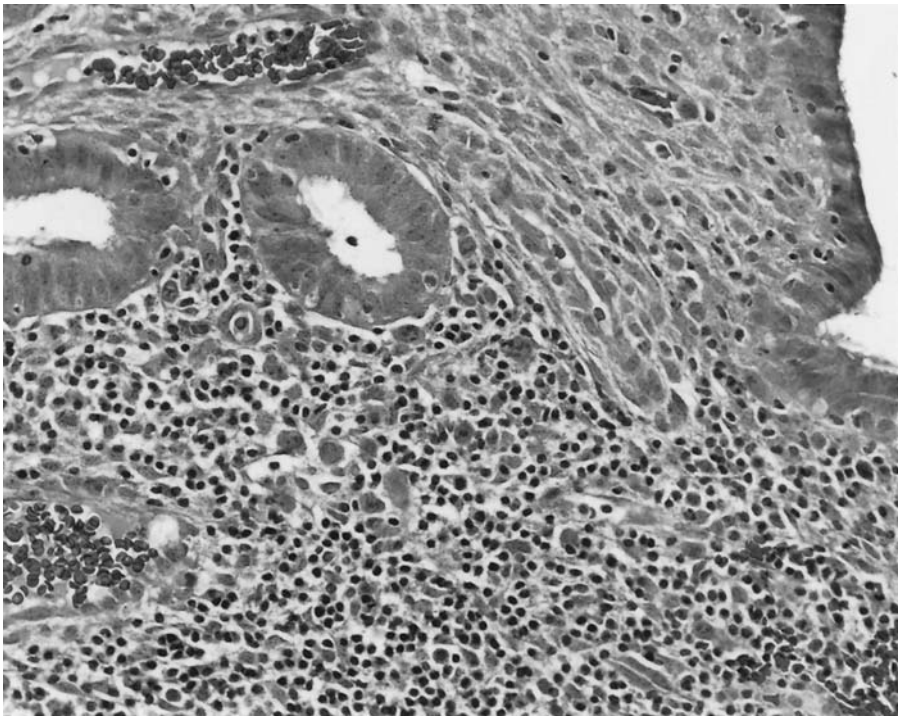

FIGURE 7.4. Nonspecific chronic endometritis. A mixed inflammatory infiltrate with scattered transformed lymphocytes and immunoblasts. Transformed lymphocytes are often associated with chlamydia infection.

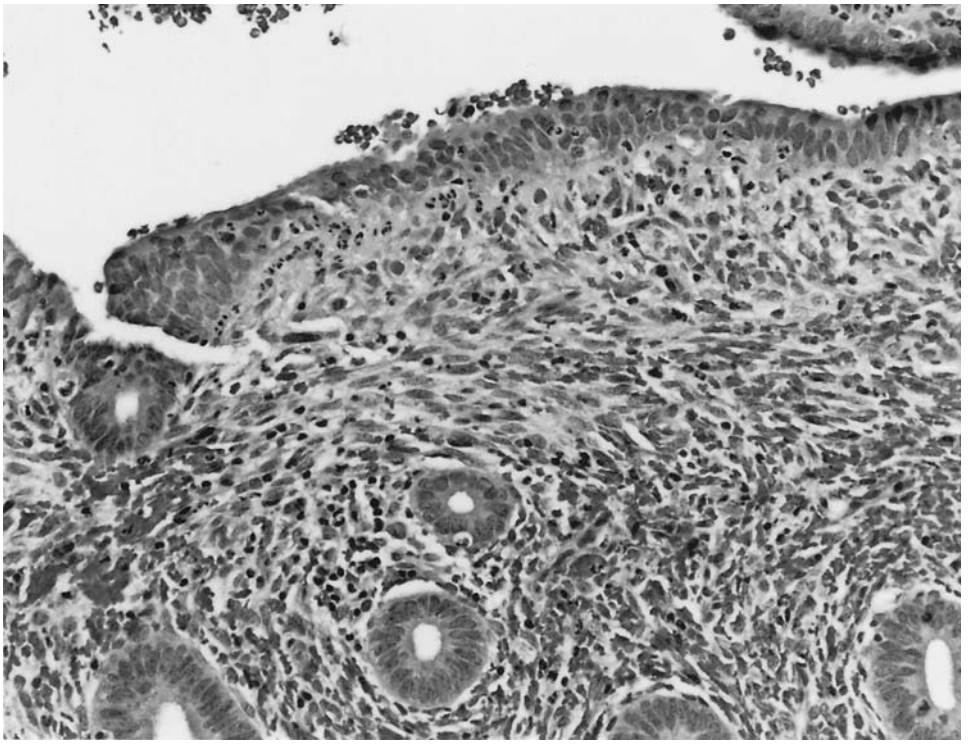

FIGURE 7.5. Nonspecific acute and chronic endometritis. Neutrophils infiltrate the surface epithelium, and the deeper stroma contains numerous lymphocytes and plasma cells.

plasma cells, must be considered before making the diagnosis of endometritis.

Acute endometritis without a chronic (plasma cell) component is extremely unusual and occurs most frequently in the postpartum or postabortal patient. Patients with pregnancy-related acute inflammation rarely come to biopsy or curettage, however. When acute endometritis is present, there is a neutrophilic infiltrate in the glands with microabscess formation and infiltration of neutrophils into the surface epithelium. Marked inflammation also will result in formation of granulation tissue with a network of small vessels in a fibroblastic stroma (Fig. 7.6).

On occasion eosinophils may be present as a part of the inflammatory infiltrate.[9] They are not normally present in the endometrium. Like lymphocytes or neutrophils, eosinophils should be present in a background of inflammatory changes to be a component of endometritis. Eosinophilic infiltrates also can occur following curettage, apparently as a result of the instrumentation,[19] and in this case they represent a nonspecific response to the procedure.

Endometritis also can have a component of histiocytes. Usually these cells are widely distributed in a mixed inflammatory infiltrate. Hemosiderin-laden stromal cells and histiocytes often are interspersed.[3;5] Sometimes histiocytes can be prominent, with large aggregates of these cells in the stroma surrounded by plasma cells and lymphocytes. When the histiocytes develop abundant, foamy cytoplasm, the process becomes xanthogranulomatous.[12;20–23]

Stromal Changes

With endometritis the stroma typically shows reactive changes.[3;9;12] Stromal cells become spindle-shaped, resembling fibroblasts, and are elongate and bipolar, in contrast to the rounded, ovoid shape of the nonreactive

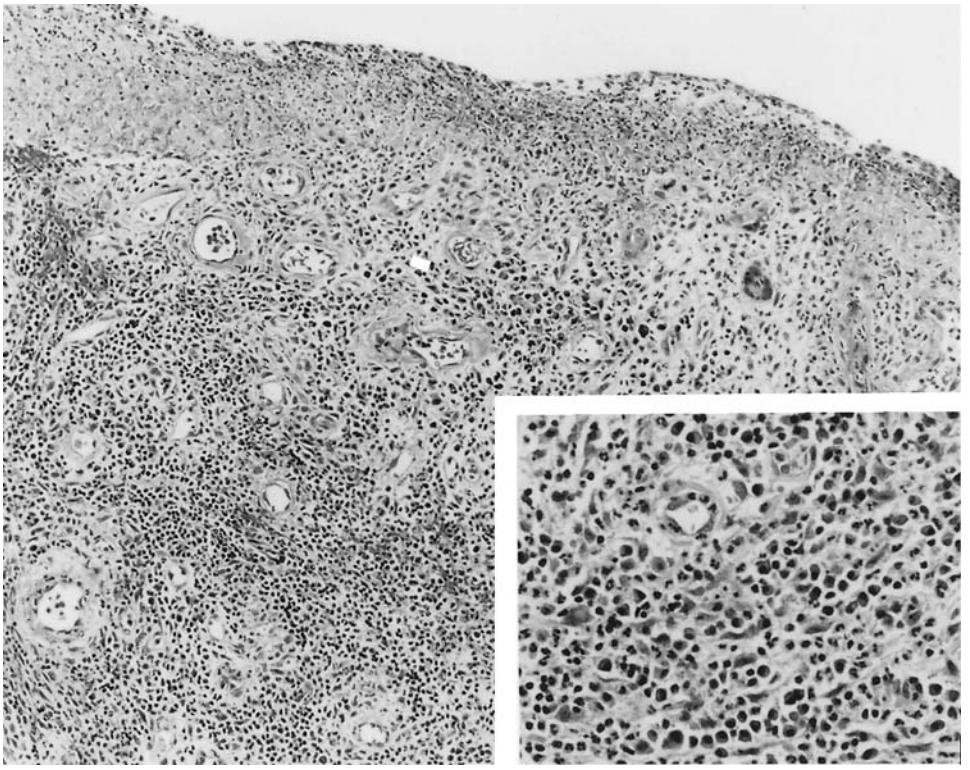

FIGURE 7.6. Acute endometritis with granulation tissue. Normal endometrium is replaced by granulation tissue composed of numerous capillaries in a dense background of inflammatory cells. The surface is ulcerated. *Inset*: The inflammation is characterized by numerous plasma cells, neutrophils, and lymphocytes.

stromal cell (see Figs. 7.1 and 7.3). The reactive process is also characterized by a swirling, interlacing pattern of the spindle cells, which may form radial, "pinwheel" arrangements (Fig. 7.7). Plasma cells usually are interspersed in the reactive stroma. Superficial stroma may become edematous.[9]

Abnormal Glandular Development

In cycling patients the endometrial response to hormones is often diminished. Usually the endometrium has proliferative phase characteristics, with tubular glands showing mitotic activity. In the secretory phase the glands may lose their normal pattern of reactivity. Secretory changes occur in ovulating women, but they often show abnormal development with less gland tortuosity and distension than is seen in a normal, noninflamed secretory phase. The changes can include irregular or retarded maturation of secretory phase endometrium. Glands may appear underdeveloped, lacking tortuosity and lumenal secretions. Plasma cells may rarely be seen in histologically normal secretory phase endometrium, however.

Epithelial Changes

Reactive cellular changes also affect the endometrial surface and glandular epithelium. The epithelium may show squamous and eosinophilic cell change (see Chapter 9), especially when the inflammation is long standing and intense.[9;10] The reactive epithelial cells may become stratified, with prominent nucleoli, cleared chromatin, and increased mitotic activity (Fig. 7.8).

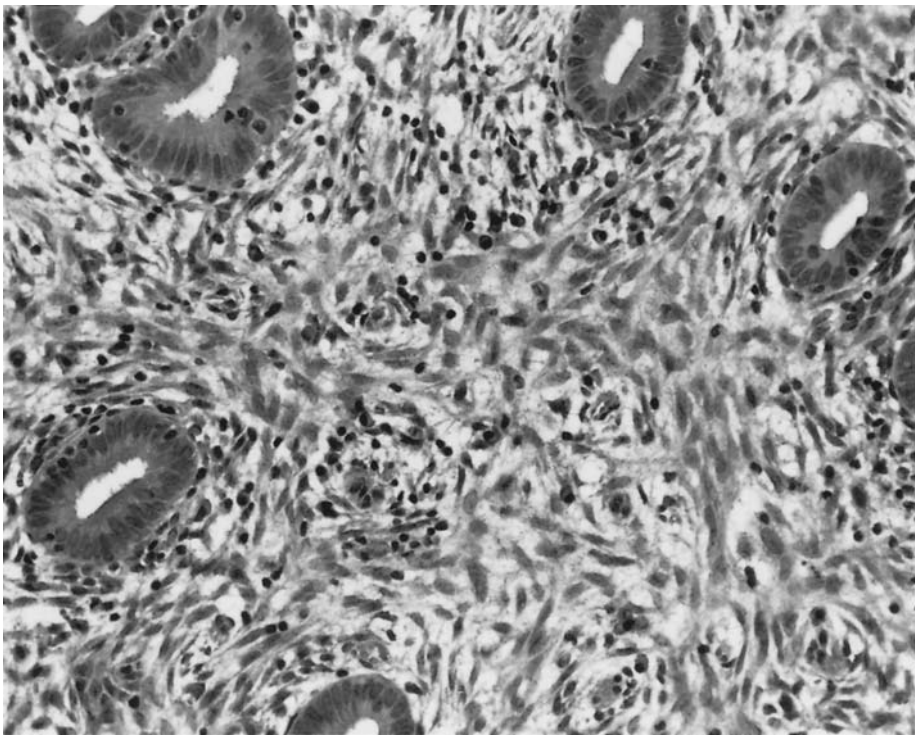

FIGURE 7.7. Nonspecific endometritis with reactive stroma. Chronically inflamed endometrium shows reactive stroma with interlacing, elongate spindle cells that resemble fibroblasts. Plasma cells and lymphocytes are interspersed.

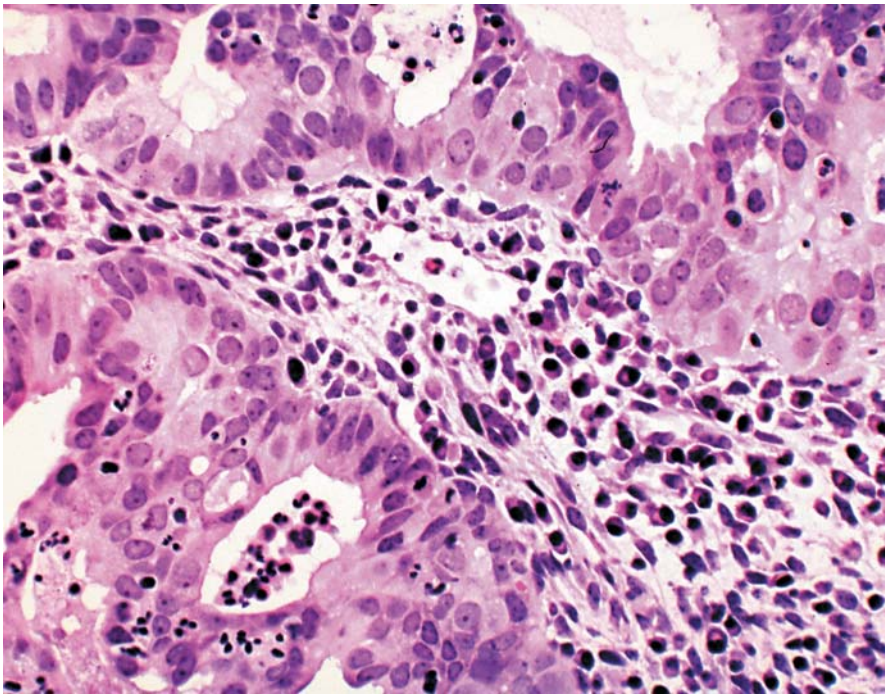

FIGURE 7.8. Nonspecific endometritis with reactive epithelial changes. The reactive glandular cells have abundant, eosinophilic cytoplasm and enlarged nuclei. A dense chronic inflammatory infiltrate with many plasma cells surrounds the glands.

Glandular and Stromal Breakdown

Endometritis also results in focal glandular and stromal breakdown. With severe and prolonged chronic inflammation, the changes of irregular bleeding with breakdown and regeneration become prominent. This pattern of haphazard bleeding leads to a corrugated surface with foci of regenerating and shedding endometrium interspersed. The inflamed stroma becomes dense and less responsive to hormonal changes. Because of the irregular growth, the tissue may become polypoid, and the resemblance to a polyp is accentuated by the dense stroma that accompanies the inflammation. A mixture of acute and chronic bleeding patterns also may be present, with areas of stromal collapse, glandular breakdown, stromal fibrosis, macrophages, and hemosiderin deposition (see Chapter 5).

Specific Infections

Although the etiology of chronic endometritis usually is not apparent in biopsy specimens, some cases show morphologic features that offer clues to the etiology. For example, the endometrium may harbor other changes, such as a retained subinvoluted implantation site following a pregnancy or abortion, a placental site nodule from a remote pregnancy, or other lesions, such as a polyp.

The inflammatory response associated with *Chlamydia trachomatis* infection is usually marked. The inflammatory infiltrate tends to be diffuse, with plasma cells, lymphocytes, and lymphoid follicles with transformed lymphocytes.[1;10;24–26] The inflammatory response to chlamydia also may be mixed, with an infiltrate of acute as well as chronic inflammatory cells. Stromal necrosis and reactive atypia of the epithelium also can be present.[10] These marked inflammatory changes are not specific for chlamydia, however, but appear to reflect the presence of upper genital tract infection and acute salpingitis.[1] One study showed that neutrophils in the endometrial surface epithelium and in gland lumens, along with a dense subepithelial stromal lymphocytic infiltrate, plasma cells, and germinal centers containing transformed lymphocytes, are features that are predictive of a diagnosis of upper genital tract infection and acute salpingitis.[1] The finding of one or more plasma cells per ×120 field in the stroma and five or more neutrophils per ×400 field in surface epithelium was strongly associated with upper genital tract infection and salpingitis.[1] *Chlamydia trachomatis* or *Neisseria gonorrheae* are most frequently associated with these findings of a marked acute and chronic inflammatory infiltrate, although infections with *C. trachomatis* produce a greater concentration of plasma cells and more lymphoid follicles than *N. gonorrheae*.[1] In cases with plasma cell endometritis, the presence of *C. trachomatis* infection can be established by using plasmid-based polymerase chain reaction (PCR) or immunohistochemistry of paraffin-embedded sections.[25;26]

Granulomatous Inflammation

Granulomatous inflammation of the endometrium is infrequent. Often the process is caused by mycobacterium, especially *Mycobacterium tuberculosis*, and the infection usually indicates advanced disease. Although rare in the United States, in some countries tuberculous endometritis is more commonly encountered in endometrial biopsies undertaken during assessment of primary or secondary female infertility, as endometrial involvement is a reflection of more widespread disease that also affects the fallopian tubes in most cases.[27;28] Tuberculous endometritis also can cause abnormal uterine bleeding in postmenopausal patients.[29] In tuberculous infection the granulomatous response is variable. Often the granulomas are nonnecrotizing.[28] Well-formed granulomas may be difficult to identify unless the endometrium is biopsied in the late secretory phase when the granulomas have had sufficient time to develop.[5;11;30] The surrounding stroma can show a lymphocytic infiltrate. As with any form of inflammation, gland development may be altered, lacking an appropriate secretory response if the biopsy is taken in the luteal phase.[30] Acid-fast stains rarely demonstrate the characteristic organism in endometrial infec-

tions, and culture of fresh tissue or PCR of paraffin-embedded tissue may be needed to establish the diagnosis.[28] Fungal infections, including cryptococcosis, coccidioidomycosis, and blastomycosis, rarely involve the endometrium, resulting in granulomatous inflammation.[4] Cytomegalovirus infection has been seen in association with poorly formed endometrial granulomas.[31] Sarcoidosis, too, may rarely lead to non-necrotizing granuloma formation in the endometrium.[32] Necrotizing granulomatous inflammation has been seen following endometrial hysteroscopic ablation therapy.[33–35] A foreign body reaction often is present in addition to the granulomas (Fig. 7.9).[35]

Actinomycosis

Infection by *Actinomyces israelii* is another rare cause of endometritis. This organism typically is found in endometritis associated with use of the intrauterine device (IUD). Use of the IUD has declined in the United States, so actinomycotic endometritis is also infrequent. When actinomycosis-associated inflammation is present, the inflammatory response usually is intense, with many plasma cells, lymphocytes, and neutrophils present throughout the tissue. The organisms show the typical sulfur granule morphology and can be stained by Gram and methenamine-silver stains.[12]

Cytomegalovirus

Rarely, endometrial biopsy will show evidence of cytomegalovirus infection. This may occur in immunosuppressed patients or it may be found in women with no known underlying disorder.[36–39] Regardless of immunologic status, the tissue shows the characteristic nuclear and cytoplasmic inclusions in epithelial cells and occasional endothelial cells (Fig. 7.10). The stroma may show a sparse plasma cell infiltrate, but other changes associated with inflamma-

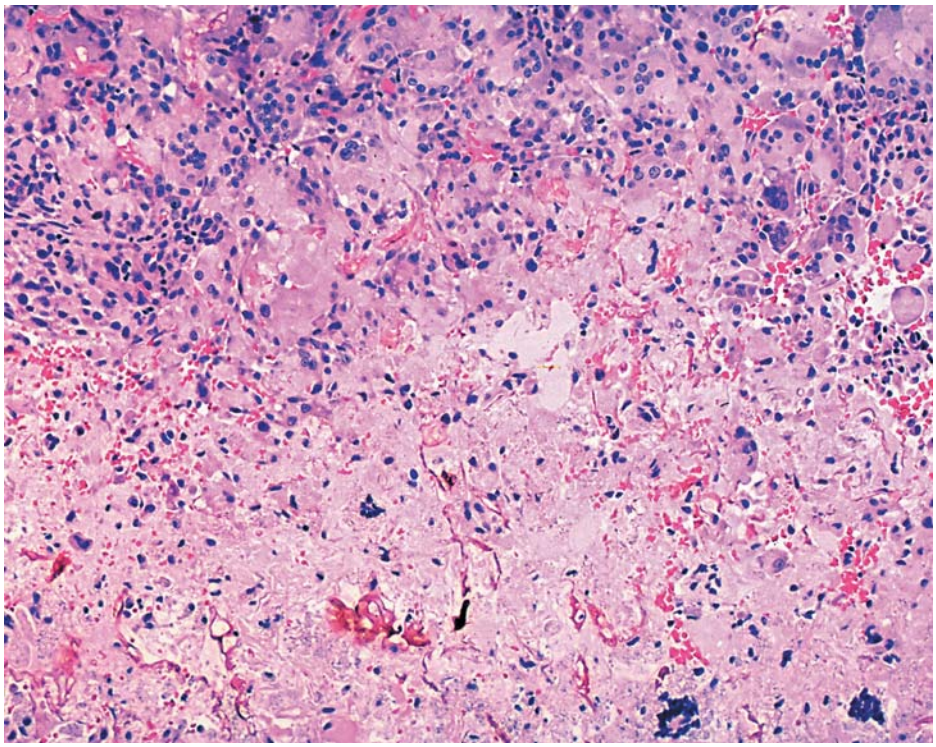

FIGURE 7.9. Foreign body granulomatous response following endometrial ablation therapy. Chronic inflammation with foreign body giant cells surround an area of necrosis. The necrotic center contains amorphous debris and carbon deposits that accumulated following thermal ablation of benign endometrium.

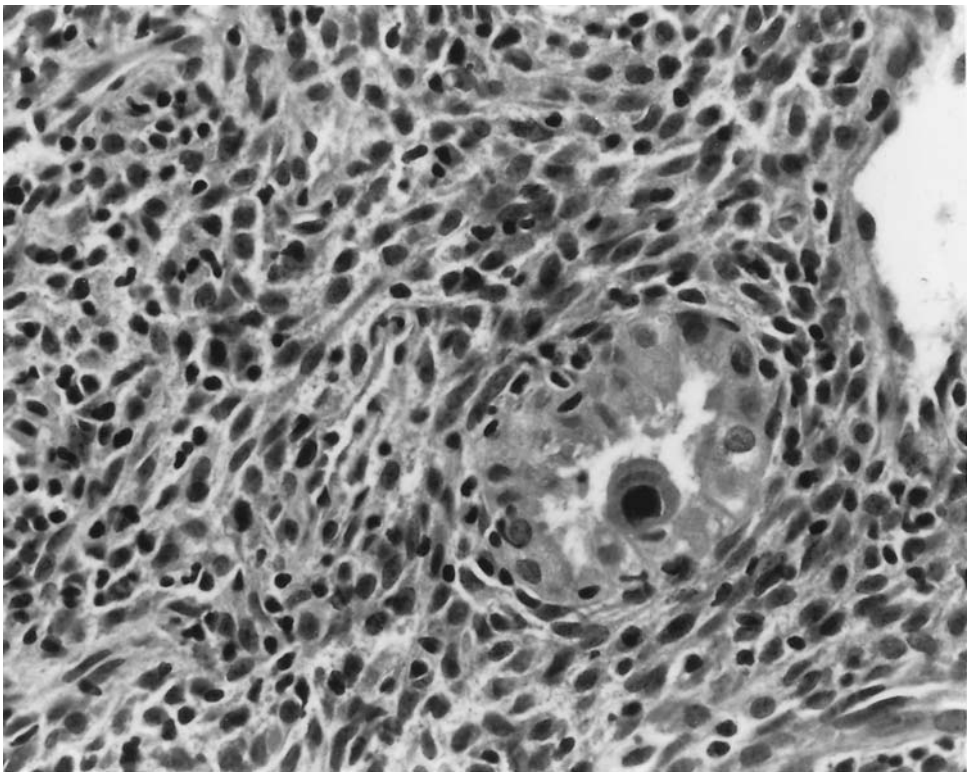

FIGURE 7.10. Cytomegalovirus endometritis. Postabortal curettage specimen shows cytomegalovirus endometritis. A single glandular cell contains a prominent dark nuclear inclusion and granular cytoplasmic inclusions.

tion, such as a spindle-cell reactive stroma, may not be found. One reported case had small, ill-defined, non-necrotizing granulomas in the endometrium but no visible inclusions, although the presence of the virus was demonstrated by PCR for viral DNA.[31]

Herpesvirus

Herpesvirus rarely infects the endometrium, but it may occur, usually as an ascending process associated with cervical infection.[40–43] When present in the endometrium, it can cause patchy necrosis of the glands and stroma (Fig. 7.11).[43] The diagnosis is established by identifying cells that show typical herpesvirus cytopathic effect. Cowdry type A inclusion and multinucleate cells with molded ground-glass nuclei can be found in the glandular epithelium or the stroma in areas of necrosis (Fig. 7.12). Several nonviral alterations, including optically clear nuclei associated with the presence of trophoblast[44] and cytoplasmic nuclear invaginations in the Arias-Stella reaction[45] (see Chapter 3), may superficially resemble the herpesvirus effect. Immunohistochemical stains for herpesvirus antigens can be helpful in documenting the presence of the virus.

Mycoplasma

The morphologic changes associated with mycoplasma, especially *Ureaplasma urealyticum*, have been described.[46;47] The inflammatory pattern, termed "subacute focal inflammation," is subtle but distinctive. In this condition the inflammatory infiltrate is patchy, focal, and difficult to discern. It is best seen in the mid-secretory phase from days 20 to 23 when stromal edema accentuates the inflammatory foci

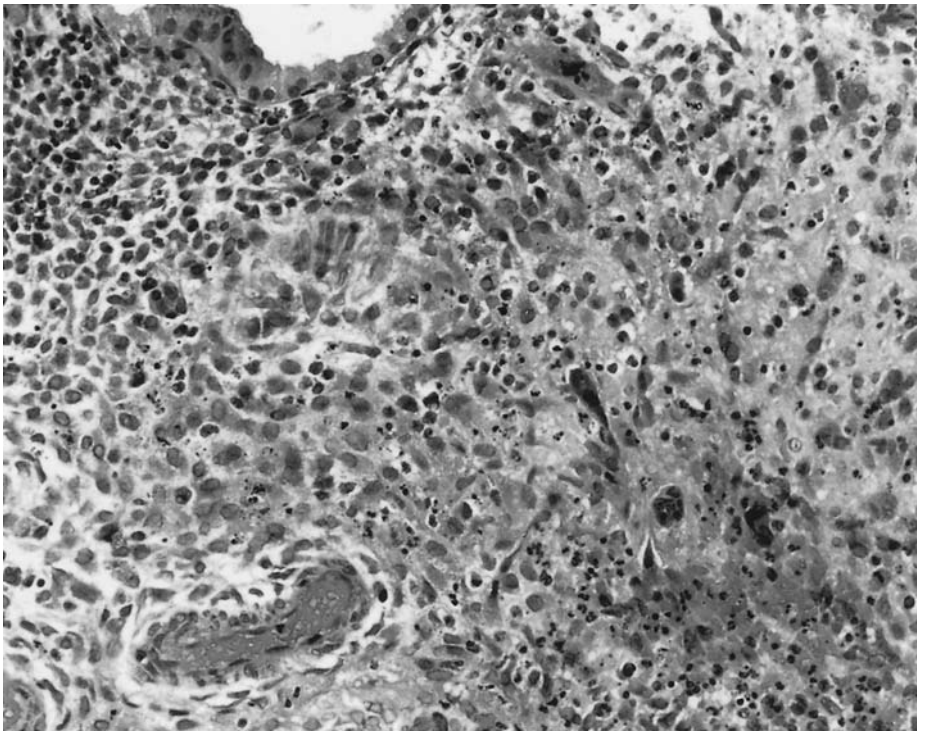

FIGURE 7.11. Herpesvirus endometritis. Area of necrosis in secretory endometrium due to herpesvirus infection. Multinucleate cells showing viral cytopathic effect are present. The patient was not immunocompromised, but herpesvirus was also present in the endocervix.

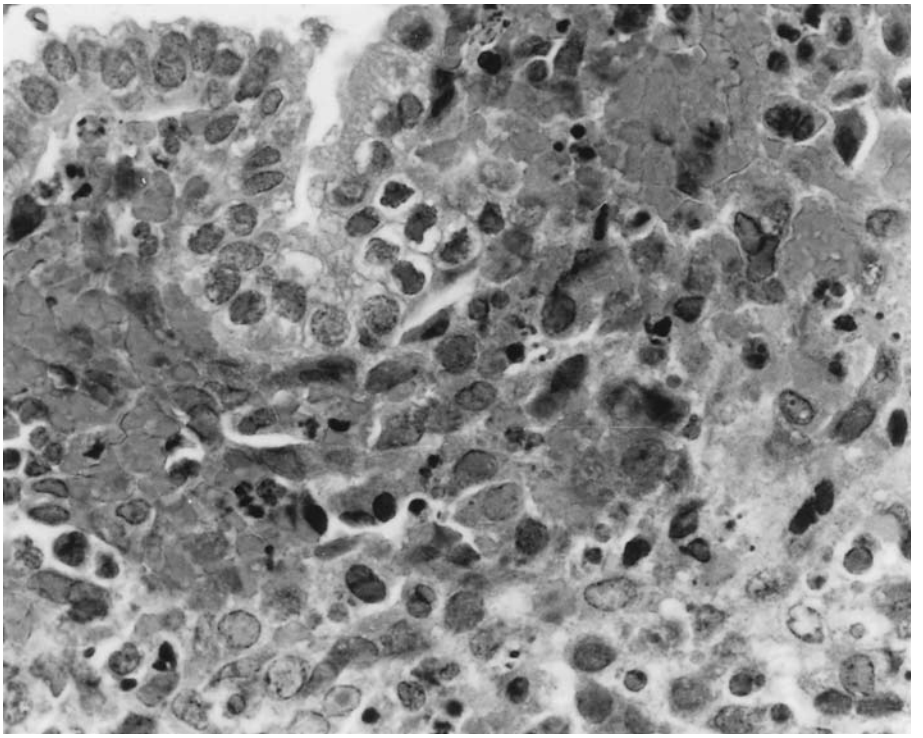

FIGURE 7.12. Herpesvirus endometritis. The nuclei of infected cells have a ground-glass appearance and contain inclusions of herpesvirus.

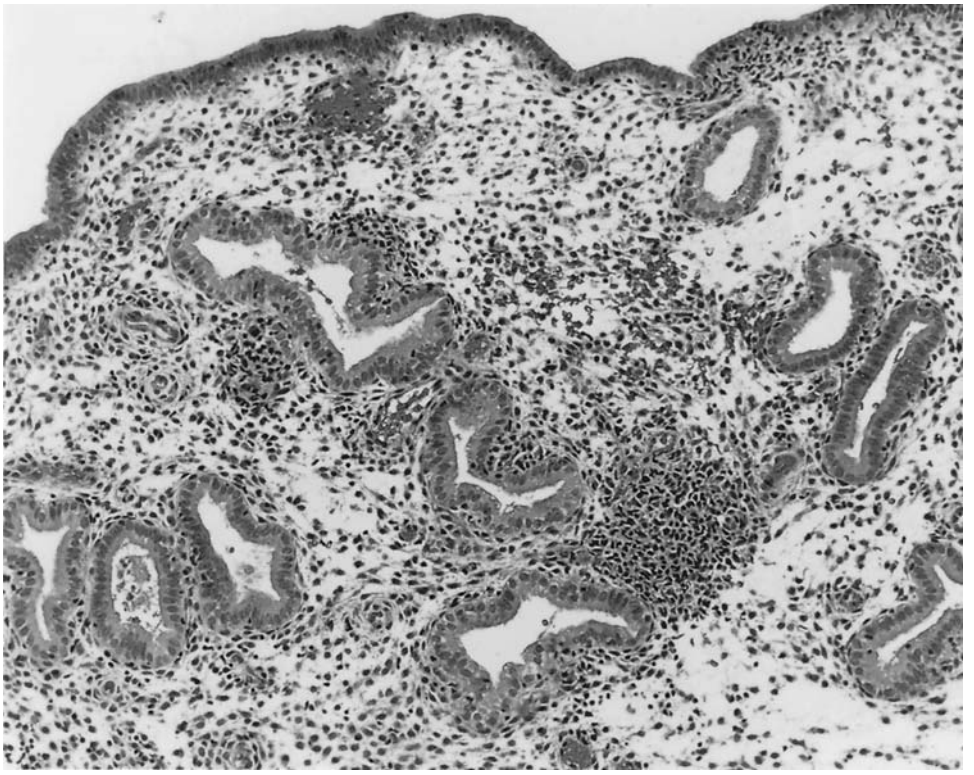

FIGURE 7.13. Subacute focal inflammation. Patchy chronic inflammatory infiltrate adjacent to glands and vessels in mid secretory endometrium. Plasma cells are sparse. This pattern is associated with mycoplasma infection.

(Fig. 7.13). The areas of inflammation consist mainly of lymphocytes with macrophages and only rare plasma cells or neutrophils.[46–48] These small inflammatory foci tend to be located beneath surface epithelium, around spiral arterioles, or adjacent to glands.[46] Chronic lesions may appear granulomatous.[46] Biopsies that are not timed for the edematous portion of the secretory phase may miss these abnormalities because the inflammatory infiltrate cannot be distinguished from normal lymphoid tissue of the endometrium. Subacute focal inflammation also has been linked with the presence of pelvic adhesions.[47]

Differential Diagnosis

One of the most difficult problems in the differential diagnosis of endometritis is to decide whether apparent inflammatory cells represent true inflammation or whether they are a part of the normal cellular infiltrate of the endometrium. Normal stromal cells can resemble plasma cells, having the same size and an eccentric nucleus. The cytologic features of the nuclei distinguish stromal cells from plasma cells, as the latter have a characteristic clock-face chromatin pattern.

Normal lymphoid aggregates and stromal granular lymphocytes can be especially difficult to distinguish from an inflammatory infiltrate, especially if the tissue is poorly preserved. Normal lymphoid aggregates, however, typically are widely spaced, located near the basalis, and do not include plasma cells. Stromal granular lymphocytes are uniformly distributed throughout the stroma and are most prominent in the late secretory phase. These cells have dark, irregular nuclei that often appear bilobed; their cytoplasm is faintly granular. Stromal granular lymphocytes normally occur in tissue

that lacks other features of inflammation, including plasma cells, reactive stroma, and glands that appear out of phase. Granular lymphocytes become especially prominent in decidualized gestational endometrium or in endometrium that shows a progestin effect, especially when the stroma shows a decidua-like reaction (see Chapter 6). In these cases the infiltrate can be so marked that at casual inspection it resembles the lymphoid response seen with endometritis. In such cases the absence of plasma cells is especially helpful in distinguishing this pattern from a true inflammatory response. The presence of decidualized stromal cells, usually containing atrophic glands showing faint secretory activity, indicates that the process is an effect of progesterone or a synthetic progestin.

Neutrophils, like lymphocytes, can be present without indicating an infectious process. They normally occur in areas of stromal necrosis associated with bleeding and in necrotic tissues such as decidua or degenerating polyps. Menstrual endometrium also shows neutrophilic infiltrates as part of the physiologic tissue breakdown. These neutrophilic infiltrates secondary to necrosis and breakdown do not represent infection. They are recognized and separated from infection-related inflammation by their lack of infiltration into the epithelium as well as their association with glandular and stromal breakdown. On occasion neutrophils also may be found only in gland lumens but not infiltrating the epithelium. This phenomenon apparently is caused by entrapment of cellular debris from a previous cycle and is a finding of no known significance.

Inflamed endocervix may also be sampled during endometrial biopsy or curettage. This tissue is a contaminant that has no relevance as long as the endometrium itself is free of an inflammatory infiltrate. Foci of nonspecific cervical inflammation usually are a minor component of the tissue in endometrial samples. Endocervical epithelium that shows squamous metaplasia or microglandular hyperplasia often is present and helps to identify these foci (see Chapter 2).

Another possible contaminant in biopsy specimens consists of aggregates of free-floating histiocytes that do not infiltrate endometrial glands or stroma. These histiocytes are a response to extracellular mucin in the endocervical canal or cellular debris in the cavity (see Chapter 2). Large sheets of histiocytes may be found in curettings following cervical stenosis with obstruction of the os. In the absence of an inflammatory infiltrate in the endometrial stroma that includes plasma cells, these free-floating histiocytes do not indicate inflammation.[49] Immunostains for histiocytes, such as lysozyme or KP-1, can be very useful for demonstrating these cells.

Pseudosulfur granules, also known as "pseudoactinomycotic radiate granules," occasionally occur in the lower female genital tract, especially in association with an IUD.[50;51] These radiate structures mimic the appearance of true actinomycotic organisms but actually represent an unusual response (Splendore–Hoeppli phenomenon) to foreign bodies or bacteria (Fig. 7.14). Pseudosulfur granules do not stain with tissue Gram stains or with methenamine-silver, whereas true actinomyces do. These peculiar structures are not associated with other endometrial abnormalities, including endometritis, and should not be mistaken for actinomycetes.

Inflamed glands may show reactive changes, with nuclear enlargement and prominent nucleoli, and the cytologic features may suggest hyperplasia or neoplasia (see Fig. 7.8). In addition, the spindle-shaped, reactive stromal cells of endometritis may be difficult to distinguish from the fibrous stroma of a polyp or from the desmoplasia of carcinoma. The architecture of tubular and uniform glands is usually preserved during inflammation, and it is important to evaluate glands in areas that do not show fragmentation or breakdown. Other underlying abnormalities, such as hyperplasia and carcinoma, may become secondarily inflamed, especially if the lesion or associated bleeding results in loss of the cervical mucus barrier or dilation of the internal os with secondary infection. These lesions should retain the typical morphology of the glands and stroma, which would allow their diagnosis in the absence of an inflammatory response. There are no data to suggest that chronic inflammation has a signif-

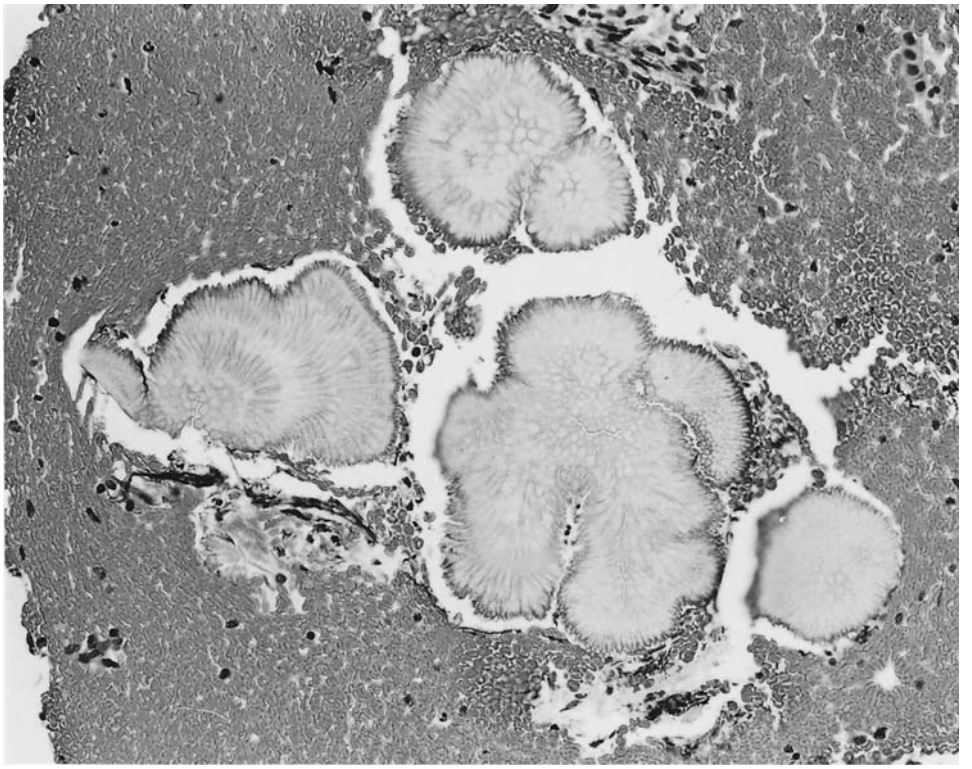

FIGURE 7.14. Pseudoactinomycotic radiate granules. These granular structures superficially resemble sulfur granules of actinomycosis. The filamentous structures are thicker than actinomycosis filaments, however, and do not stain for organisms with Gram or silver stains. The patient had an IUD in place at the time of the biopsy. The endometrium was not inflamed.

icant relationship to the genesis of either hyperplasia or carcinoma of the endometrium. Polyps should be localized abnormalities with at least a partial lining of surface epithelium, and these generally do not contain plasma cells unless they are secondarily inflamed as a result of extension into the endocervix.

Severe chronic endometritis can produce an intense lymphoid infiltrate with large lymphoid cell immunoblasts that can resemble signs of malignant lymphoma or a leukemic infiltrate.[16–18] Usually with severe inflammation, the cellular infiltrate is mixed, with a combination of plasma cells, neutrophils, and lymphoid cells with follicle formation, whereas lymphoma or leukemic infiltrates usually are composed of a relatively monotonous cell population. Involvement of the endometrium by malignant lymphoma is rare in the absence of disseminated disease. The most common hematologic malignancy to involve the endometrium is non-Hodgkin lymphoma, usually the diffuse large-cell type, but this is a rare finding in biopsy specimens (see Chapter 11).

Clinical Queries and Reporting

Accurate diagnosis of endometritis is important, as the presence of inflammation can establish a cause for abnormal bleeding or unexplained infertility. Most cases of endometritis have no specific etiology that can be determined by histologic study of the biopsy specimens. When endometritis is present, however, a statement to indicate whether the sections also show a demonstrable cause of the inflammation, such as evidence of a recent pregnancy or an organic lesion, such as a polyp, may be helpful for subsequent clinical manage-

ment. The presence of such lesions helps to establish the clinical cause and significance of the inflammation.

The intensity of the inflammation also should be noted, especially as severe inflammation with neutrophils in the surface epithelium, a dense subepithelial stromal lymphocytic infiltrate, and lymphoid follicles with transformed lymphocytes raises the possibility of upper genital tract inflammation and salpingitis.

Specific infections, such as tuberculosis or cytomegalovirus, should clearly be indicated when they are present. If special stains for organisms are performed, the results should be given in the report.

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