Calciphylaxis causes calcification, thrombosis, cutaneous ischemia, and necrosis in the skin and subcutaneous tissue. It is unclear to what extent it involves other organs. To identify whether other organs are affected we reviewed pathology reports of patients with calciphylaxis who underwent autopsy at Mayo Clinic, Rochester, Minnesota, between January 1, 1970, and December 31, 2011. Three patients were identified: two patients had a diagnosis of end-stage renal disease secondary to diabetes mellitus before the diagnosis of calciphylaxis; the third patient had calciphylaxis associated with metastatic cholangiocarcinoma without end-stage renal disease. Autopsy reports showed that despite evidence of vessel calcification elsewhere, there was no evidence of calciphylaxis in other organs. All patients had histopathologic evidence of cardiovascular calcification, and atherosclerosis of coronary arteries and aorta. Calcification of pancreatic vessels and renal vessels was also noted. In this study population, calciphylaxis was a cutaneous process alone.

Key words: autopsy; calcific uremic arteriolopathy; calciphylaxis.

Methods
We used the institutional medical index and text retrieval system to identify patients who 1) had received a diagnosis of calciphylaxis, calcific uremic arteriolopathy, vascular calcification, cutaneous necrosis syndrome, or calcifying panniculitis; and 2) underwent autopsy at Mayo Clinic, Rochester, Minnesota, between January 1, 1970, and December 31, 2011. Patients were excluded if they had denied research authorization or did not meet inclusion criteria. The Mayo Clinic Institutional Review Board approved this study. We reviewed all autopsy reports and microscopically examined representative archived tissue sections from extracutaneous organs reported to have calcification.
Calciphylaxis as a cutaneous process

Definition of calciphylaxis
For the purposes of this study, we defined calciphylaxis as the clinical findings of indurated patches with ischemia or infarction and ulceration, with supportive histopathologic findings of tissue ischemia and necrosis due to arteriolar calcification, extravascular calcification, intimal fibroplasia, and thrombosis (1).

RESULTS

Description of patients studied
Three patients (2 women; 1 man) met the study inclusion criteria. The mean ± SD age at onset of calciphylaxis was 58.3 ± 5.1 years. Two patients had been diagnosed with end-stage renal disease secondary to diabetes mellitus before developing calciphylaxis. Both of these patients had been treated with hemodialysis. The third patient received a diagnosis of calciphylaxis associated with metastatic cholangiocarcinoma without end-stage renal disease. The treatment of this patient was previously described previously (11).

Antemortem skin biopsies substantiated a clinical diagnosis of calciphylaxis in all 3 patients (Fig. 1). Survival after diagnosis of calciphylaxis ranged from 19 to 331 days. The mean ± SD age at death was 58.7 ± 5 years. All 3 patients died from serious infections. Two of the study patients had sepsis due to necrotic skin ulcers. The third patient developed sepsis due to pneumonia. Table I summarizes the clinical characteristics of the 3 patients. Fig. 2 shows the clinical presentation of calciphylaxis in each of the 3 patients.

Autopsy reports

Autopsy reports are summarized in Table II.

Skin involvement: Skin biopsies were consistent with calciphylaxis. Anatomic distribution of calciphylaxis was reported on autopsy as involving upper extremity (n = 1), torso (n = 1), and lower extremity (n = 3).

Systemic involvement: Representative archived tissue sections from extracutaneous organs reported to have calcification were examined microscopically: none had histologic evidence to support calciphylaxis of the extracutaneous organs: specifically, none had evidence of extravascular calcification, vessel thrombosis, tissue ischemia, or luminal fibrosis.

The autopsy reports indicated that all 3 patients had histopathologic evidence of cardiovascular calcification (Fig. 3a), and atherosclerosis of the coronary arteries and aorta. Calcification of pancreatic vessels (n = 1) and renal vessels (n = 1; Fig. 3b) was also noted. Two patients had annular calcification of the heart valves (mitral [n = 2] and aortic [n = 1]).

Thus, although vessel calcification was identified in other organs, other microscopic features of calciphylaxis were not reported to be present in organs other than the skin.

Table I. Characteristics of the 3 patients with calciphylaxis who were autopsied after death

<table>
<thead>
<tr>
<th>Pat. No./Sex</th>
<th>Age at onset</th>
<th>Age at death</th>
<th>Medical history</th>
<th>Dialysis</th>
<th>Antemortem skin biopsy</th>
<th>Survival after diagnosis, days</th>
<th>Primary cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F</td>
<td>64</td>
<td>64</td>
<td>End-stage renal disease; diabetes mellitus type 2; hypertension; stable coronary artery disease</td>
<td>Yes</td>
<td>Yes</td>
<td>33</td>
<td>Sepsis due to necrotic calciphylaxis skin ulcers</td>
</tr>
<tr>
<td>2/M</td>
<td>57</td>
<td>58</td>
<td>End-stage renal disease; insulin-dependent type 2 diabetes; hypertension; dilated cardiomyopathy; antiphospholipid syndrome; hypothyroidism; alcoholism; penile gangrene; amputation at knee</td>
<td>Yes</td>
<td>Yes</td>
<td>331</td>
<td>Sepsis due to pneumonia</td>
</tr>
<tr>
<td>3/F</td>
<td>54</td>
<td>54</td>
<td>Metastatic cholangiocarcinoma; diabetes mellitus type 2; deep vein thrombosis; frontal subdural hematoma</td>
<td>No</td>
<td>Yes</td>
<td>19</td>
<td>Sepsis due to necrotic calciphylaxis ulcers</td>
</tr>
</tbody>
</table>

Fig. 2. The clinical presentation of calciphylaxis in each of the 3 patients. Lesions mainly on right buttock of Patient 1 (a). Lesions on left lower leg of Patient 2 (b). Lesions on both thighs of Patient 3 (c).
DISCUSSION

The histopathologic diagnosis of calciphylaxis in any organ system requires the presence not only of vascular and tissue calcification but also of associated tissue necrosis. Other findings, such as vascular occlusion by thrombi and intraluminal fibrosis, may support the diagnosis. Calcification in unusual anatomical locations or that it is extensive is insufficient for a diagnosis of systemic calciphylaxis. Calciphylaxis was identified only in the skin of these 3 patients. Although intravascular calcium deposition was noted in other organs, associated tissue ischemia or necrosis (as required for calciphylaxis) was not reported. The extracutaneous calcium deposition noted postmortem in these patients was related to comorbidities, including diabetes mellitus, atherosclerosis, and end-stage kidney disease. Therefore, although patients with calciphylaxis not surprisingly have systemic evidence of chronic cardiovascular stress and injury, the pathophysiology of calciphylaxis appears to have been confined to the skin in these patients.

We chose to study the autopsy data from these patients because postmortem examination is more thorough and systematic than antemortem physical examination, biopsy findings, or imaging studies. Scattered case reports have reported autopsy findings in patients with calciphylaxis (Table III) (6–8, 11–21). The vast majority of the reports document vascular calcification but not calciphylaxis of these internal organs (defined as in methods); in only 2 case reports would criteria perhaps fit with these criteria. One reported “extensive vascular calcium deposition within multiple mesenteric vessels in the small bowel, with full-thickness necrosis; also in the dura” (7), and another reported “diffuse medial calcification, with intimal fibrosis and cellular thickening, partly accompanied by microthrombi involving small- to medium-sized visceral arteries” (8). Without reviewing this reported pathology, it is difficult to confirm whether or not these findings truly represented calciphylaxis of these organs.

Other reports have noted “visceral calciphylaxis” in patients on whom an autopsy was not performed or reported (9, 10). These patients had antemortem biopsies from extracutaneous organs that showed findings said to be consistent with calciphylaxis in the lungs and gastrointestinal tract. In most of these cases, calcium deposition was noted systemically, but microscopic criteria that would satisfy a diagnosis of calciphylaxis were not described. This raises the possibility that it was intra- and/or extra-vascular calcification alone that was identified rather than calciphylaxis in organs other than the skin.

The pathogenesis of calciphylaxis is not well understood. The term was coined by Hans Selye (22) in 1962 to describe skin necrosis that was provoked by exposure to substances such as parathyroid hormone and vitamin D, and it was associated with cutaneous calcification in experimental animals. The pathogenic mechanism of calciphylaxis has since been likened to “the skin equivalent of a myocardial infarction,” since vessel narrowing by intravascular calcification and fibrosis leads to tissue ischemia after an acute event such as thrombo-occlusion (23). While vascular mural calcification is not sufficient for a diagnosis of calciphylaxis, mural calcification does appear to be an early and essential process in the development of a calciphylaxis plaque. In one postmortem study, an incisional skin biopsy specimen from a patient with calciphylaxis showed subcutaneous vascular mural calcification, extravascular calcification, which exten-
### Table III. Published case reports describing postmortem results of patients with calciphylaxis

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Patient age, years/Sex</th>
<th>Kidney involvement</th>
<th>Endothelial deposition</th>
<th>Cause of death</th>
<th>Cutaneous involvement</th>
<th>Cause of death</th>
<th>Metastatic calcification</th>
<th>Autopsy reports (calciphylaxis or calcification?)</th>
<th>Partially</th>
<th>Cause of death</th>
<th>Autopsy pathology</th>
<th>Cause of death</th>
<th>Cause of death</th>
<th>Autopsy pathology</th>
<th>Cause of death</th>
<th>Autopsy reports (calciphylaxis or calcification?)</th>
<th>Partially</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conn et al. (1973) (6)</td>
<td>23/F</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Sepsis</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Asmundsson et al. (1988) (16)</td>
<td>25/F</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Sepsis</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Edelstein et al. (1992) (20)</td>
<td>50/M</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Cardiac arrest</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Tamura et al. (1995) (8)</td>
<td>50/F</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Sepsis</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Sepsis</td>
<td>Yes</td>
<td>Yes</td>
<td>Sepsis</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>McAuley et al. (1997) (15)</td>
<td>46/M</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Cardiac arrest</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Sepsis</td>
<td>Yes</td>
<td>Yes</td>
<td>Sepsis</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>McAuley et al. (1997) (15)</td>
<td>48/M</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Cardiac arrest</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Sepsis</td>
<td>Yes</td>
<td>Yes</td>
<td>Sepsis</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Brown et al. (1998) (13)</td>
<td>38/F</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Cardiac arrest</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Sepsis</td>
<td>Yes</td>
<td>Yes</td>
<td>Sepsis</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Oh et al. (1999) (12)</td>
<td>54/M</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Sepsis</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Klopert et al. (2003) (19)</td>
<td>53/F</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Sepsis</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Suryadevara et al. (2008) (21)</td>
<td>11/M</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Sepsis</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Volpini &amp; Kinonen (2011) (7)</td>
<td>43/F</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Cardiac arrest</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Matsuo et al. (2001) (18)</td>
<td>57/M</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Riegert-Johnson et al. (2001) (11)</td>
<td>54/F</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

| Table III. Publish single case reports describing postmortem results of patients with calciphylaxis. |

**Notes:**
ded peripherally by as much as 3 cm, and thromboses within the dermis and subcutis (24).

We acknowledge the limitations of this review, including its retrospective design, the small number of patients with calciphylaxis who had autopsy and thus met inclusion criteria, and the possible selection bias of including only those patients on whom an autopsy had been performed. We recognize that it is difficult to extrapolate findings from 3 cases.

We conclude that in the study population, calciphylaxis was a cutaneous process alone and did not involve other organs. Our study is of just 3 patients: further autopsy studies from patients with calciphylaxis are needed to confirm or refute our findings that calciphylaxis only involved skin and does not seem to involve extracutaneous organs.

The authors declare no conflicts of interest.

REFERENCES