# Morphologic Markers of Acute and Chronic Stress in Child Abuse

*Mark A. Flomenbaum, MD, PhD,*[1] *and Ryan C. Warner*[2]

From the [1]Office of Chief Medical Examiner, Augusta, ME, USA; and [2]Larner College of Medicine, University of Vermont, Burlington, VT, USA.

## ABSTRACT

**Objectives:** To elucidate pathologic markers of acute and chronic stress found but rarely reported in chronic child abuse.

**Methods:** Autopsies of 3 cases of fatal child abuse with well-documented chronic maltreatment are reported, with an emphasis on the nontraumatic findings of acute and chronic stress.

**Results:** Besides the overwhelming physical injuries, all 3 children and 1 additional case obtained for consultation had telogen effluvium, a form of alopecia well known to be associated with stress in adults and some children but never reported in chronic abuse. All 3 had the microscopic findings of markedly involuted thymus, a well-known marker of physiologic stress in children but only occasionally referred to in child abuse. All 3 also had microscopic findings of myocardial necrosis associated with supraphysiologic levels of catecholamine, a well-documented finding associated with stress but rarely reported in fatalities associated with child abuse. Two of the 3 children also had Anitschkow-like nuclear changes in cardiac tissue, markers associated with prior, nonischemic myocardial pathologies that may be associated with prior episodes of acute stress.

**Conclusions:** Pathologists are urged to explore these markers as supportive evidence in their own investigations of possible child abuse fatalities, especially when associated with stress.

## INTRODUCTION

Despite widespread public attention and mobilization of considerable resources to address the issue, child fatalities resulting from abuse and neglect have trended up in recent years. The US Administration for Children and Families reports that in 2019 an estimated 1,840 children died as a result of abuse or neglect, up nearly 200 from 5 years earlier.[1] As part of a multiprong approach to reverse this trend, it is critical that caseworkers, law enforcement officers, pediatricians, emergency physicians, pathologists, and all other mandated reporters be given new tools to identify and better categorize potential abuse cases. We examined 3 cases of fatal chronic child abuse and neglect (2.5, 4, and 10 years of age, all girls) and report pathologic findings that are often not described in stress-related chronic child abuse deaths.

On gross examination, we noted that all 3 victims had multiple bruises over multiple body segments that varied in appearance by color and the sharpness of their edges FIGURE 1, FIGURE 2, and FIGURE 3. Bruises (also called contusions) are the result of blunt trauma, where the force does not break the surface skin but causes visible subcutaneous hemorrhage from injured capillaries and other small vessels. As the body tries to heal, the exsanguinated blood is metabolized through well-defined pathways.

## KEY POINTS

- We describe morphological markers of acute and chronic stress that have rarely been described and are underreported in cases of fatal chronic child abuse.
- Being aware of these findings can help pathologists and clinicians understand the context in which other trauma or stressors may occur.
- Some findings may be evident during life and may be useful for the prevention of fatalities.

## KEY WORDS

Child abuse; Stress; Catecholamines; Telogen effluvium; Thymic involution; Myocytolysis; Anitschkow

*Am J Clin Pathol* June 2022;157:823-835
HTTPS://DOI.ORG/10.1093/AJCP/AQAB204

Received: August 17, 2021
Accepted: November 5, 2021
Advance publication: December 17, 2021

Corresponding author: Mark Flomenbaum, MD, PhD; mark.flomenbaum@maine.gov.

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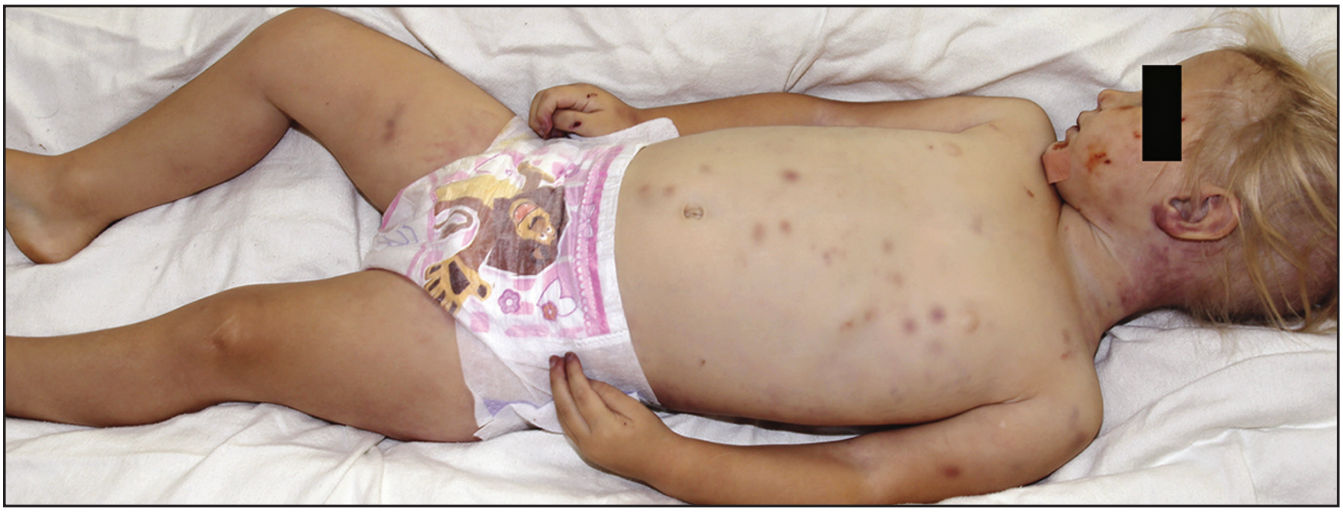

**FIGURE 1** Overall photo of case 1, a 2.5-year-old girl.

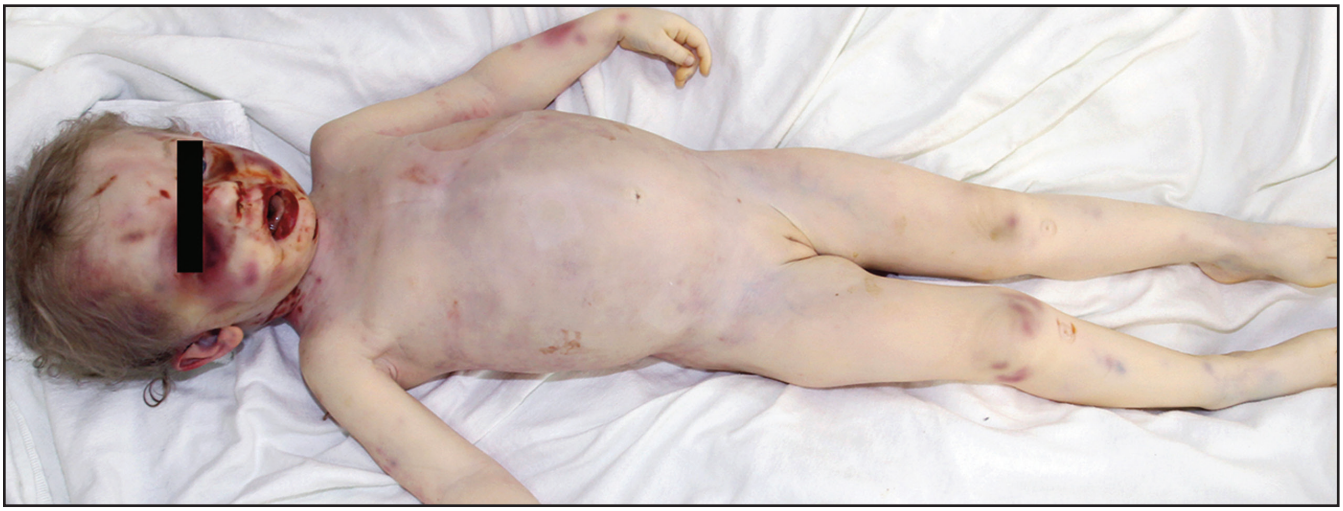

**FIGURE 2** Overall photo of case 2, a 4-year-old girl.

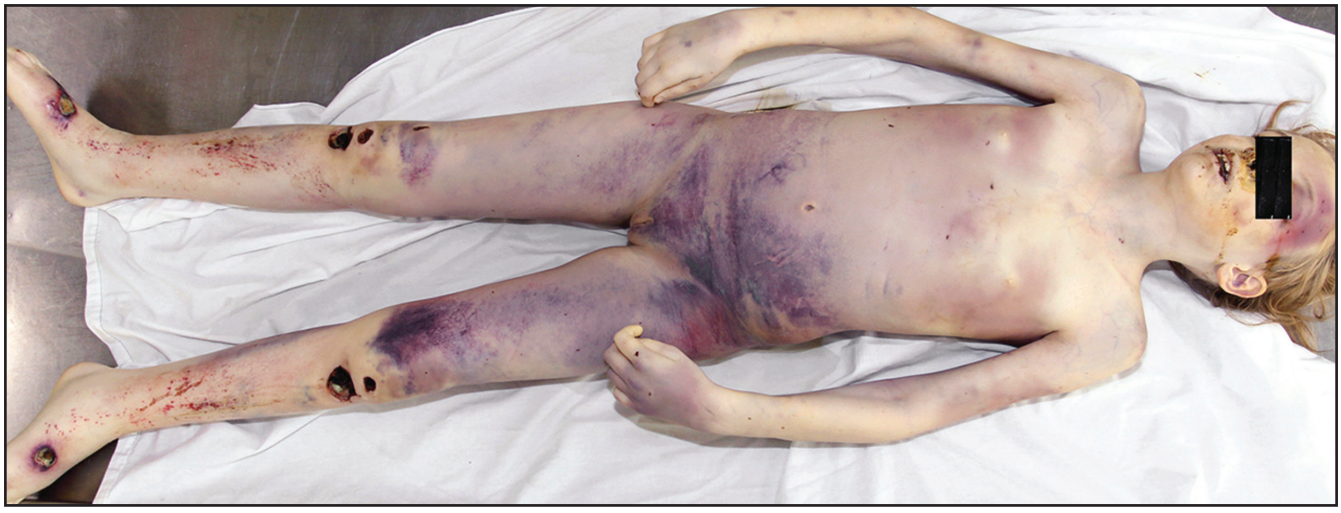

**FIGURE 3** Overall photo of case 3, a 10-year-old girl.


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Bruises are initially reddish blue or purple and become bluish brown in 1 to 3 days. Their color then changes successively to greenish brown, greenish yellow, yellowish brown, tan, and yellow before normal skin color reappears. Color changes and fading start peripherally and extend centripetally; complete resolution can require 1 to 3 weeks.[2]

In addition to the obvious severe blunt trauma, all 3 children had a specific type of alopecia known as telogen effluvium. This condition has been widely reported as a result of stress, especially in adults,[3] but never in chronic child abuse. Microscopic examinations in all 3 cases showed marked thymic involution, a well-known characteristic of chronic physiologic stress.[4] All 3 children had histologic evidence of nonischemic cardiac damage, including single-cell myocyte necrosis. Supraphysiologic catecholamine levels are widely reported as an acute physiologic response to stress,[5] and cardiac pathologies are well documented as morphologic changes resulting from acute stress, with elevated catecholamine levels.[5-7] We posit that our findings are consistent with response to stress but rarely reported in cases of child abuse and almost never in association with each other. The older 2 children also had foci of single-cell cardiomyocyte hypertrophy and Anitschkow-like nuclear patterns in cardiomyocytes and interstitial cells. We believe that these cellular and nuclear changes are nonspecific reactions to either markedly compromised or dead myocytes and with exclusion of other known cardiac pathology may represent prior catecholamine-induced myocytolysis as the etiology of this manifestation.

We present the histories and autopsy findings of these 3 cases, with relevant literature pertinent to our major findings. The detailed microscopic findings of the thymus and heart are presented collectively rather than separately for each case to facilitate more coherent discussion of the topics.

We in no way consider our literature reviews to be exhaustive, nor do we believe that our cases are representative of all victims of chronic child abuse. We are presenting individual findings and the concurrence of those findings, which may not have been considered in previous investigations. We urge all practitioners involved in child welfare to be aware of these findings to aid in their own investigations.

## MATERIALS AND METHODS

In each of the 3 cases we reviewed all available medical and emergency medical services records, reports from child protective agencies, and reports from law enforcement agencies. Complete forensic autopsies were performed, including both gross and microscopic examinations, toxicology, and other relevant laboratory testing. All major organs and representative samples of injuries were examined microscopically to evaluate natural disease (if present) and to provide more details of the injuries. For these cases, the minimum number of sections examined for the hearts was 10, for the thymuses was 4, and for the scalps was 2.

### Case 1

A 2.5-year-old girl was found unresponsive in the morning by her father and his girlfriend. (Law enforcement reports a history of domestic abuse between the decedent's father and her biological mother.) Responding officers reported that the residence was extremely filthy, reeking of animal feces, urine, and marijuana, and had flies hovering over rotting food. Detectives also reported that neither adult could articulate when the child had last been bathed, last had her diaper changed, or last eaten. A review of her medical history showed that in the months before her death, her weight-for-age had dropped from the 72nd percentile to the 32nd percentile, and her weight-for-length dropped from the 68th percentile to the 37th percentile.

#### Autopsy Findings

The scalp had large patches of balding, with hair easily shed with minimal manipulation of the head FIGURE 1 and FIGURE 4. The scalp was otherwise free of visible pathology. There were multiple instances of blunt-force trauma to the rest of the body, including multiple contusions and abrasions of the head, neck, and extremities. Internally, there was transection of the gastrointestinal junction, partial transection of the pancreas, 320-mL hemoperitoneum (measured), and lacerations of lumbosacral prevertebral fascia. The weights and measures are itemized in TABLE 1.

#### Microscopic Findings

Microscopically, there was no pathology at the balding areas of the scalp. Most of the trauma was accompanied by fresh hemorrhage, with little or no inflammation or other attempt at resolution, indicating recent occurrence. Other sites had some hemosiderin-laden macrophages or granulation tissue indicative of prior events. There was marked involution of the thymus FIGURE 5A and FIGURE 5B. Cardiac findings included bands of hypereosinophilic myocytes and isolated myocytic coagulative necrosis FIGURE 6A and FIGURE 7A. Newborn screening blood spot testing for 17-hydroxyprogesterone (17-OHP) was 7.1 ng/mL. Toxicologic and microbiologic testing were noncontributory. The cause of death was signed out as "Blunt force trauma of torso with multiple organ lacerations and hemoperitoneum."

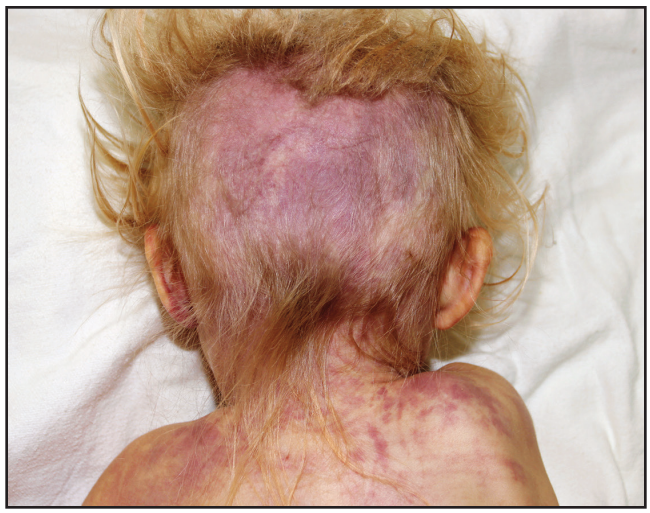

**FIGURE 4** Scalp of case 1.




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**TABLE 1** Summary of Autopsy Weights and Measures

| Case No. | Age/ Sex | Height, cm | Weight, kg | Brain, g | Heart, g | Lungs (Combined), g | Liver, g | Spleen, g | Thymus, g | Kidneys (Combined), g |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 y, 5 mo/F | 89 | 12.2 | 1,090 | 57 | 153 | 380 | 42 | 7.12 | 80 |
| 2 | 4 y, 0 mo/F | 88 | 13.3 | 1,110 | 89 | 304 | 503 | 29 | 13.0 | 91 |
| 3 | 10 y, 3 mo/F | 145 | 34.5 | 1,200 | 150 | 910 | 1,050 | 80 | – | 170 |

F, female.

### Case 2

A 4-year-old girl had a life-long history of neglect and indications of approximately 20 months of abuse, with at least 3 reports to Child Protective Services. Parental rights were forfeited soon after birth (because of parental drug involvement), and the decedent was placed in the custody of a family member, where she lived for approximately 20 months before her death. The caregivers reported at the time of death that bruises began to appear on the girl's face because "she was accident prone," and they therefore kept her out of public view.

#### Autopsy Findings

The scalp had spotty hair loss and clumps of hair easily removable with minimal efforts; the scalp was free of any visible pathologic etiology for the hair loss FIGURE 2 and FIGURE 8. There were multiple instances of blunt-force trauma to her head (15-20 distinct injuries, including a palpable hard "ridge" below the occipital scalp), neck, and extremities (11 distinct injuries), with radiologic indication of free air in the abdomen. Internally, she had lacerations of the pancreas, mesocolon, and gastrocolonic membranes, with hemoperitoneum (approximately 350-500 mL); cerebral edema; and pulmonary edema. The weights and measures are itemized in TABLE 1.

#### Microscopic Findings

Microscopic examination indicated no scalp pathology other than trauma. Most of the trauma was accompanied by fresh hemorrhage, with little or no inflammation or other attempt at resolution. The subscalpular occipital "ridge" was composed of dense and soft fibrous tissue with maturing fibroblasts, mesenchymal cells, and neovascularization consistent with scar formation from prior trauma. There was marked thymic involution of the cortex with diffuse interstitial fibrosis FIGURE 5C and FIGURE 5D. The heart had partially cytolyzed myocytes, with indication of coagulative necrosis, bands of acute hypereosinophilic myocytes, random single-cell contraction banding, and random hypertrophic myocytes sometimes in disarray FIGURE 6B, FIGURE 7B, FIGURE 7C, and FIGURE 7D. An Anitschkow-type chromatin pattern was seen in some myocytes and interstitial cells FIGURE 9A, FIGURE 9B, and FIGURE 9C. Newborn screening blood spot test for 17-OHP was 10.8 ng/mL. Toxicologic and microbiologic testing were noncontributory.

The cause of death was signed out as "Blunt force trauma of abdomen with laceration of pancreas and hemoperitoneum," and "Multiple blunt force trauma to head with subscalpular hemorrhage" was listed as a contributory factor.

### Case 3

A 10-year-old girl suffered at least 5 months of well-established abuse, including being locked in a small closet daily for hours at a time and being forced to kneel on a rough tile floor while being struck repeatedly, once even having a metal mop handle break across her ribs. The beatings continued daily until just before she died, when she could no longer walk and could no longer talk without slurring her speech, at which time one of the abusers admitted to beating her even harder, believing that the child was faking. At the scene of her death, police reported extensive bruising across her head, abdomen, and legs as well as multiple open wounds to her knees.

#### Autopsy Findings

On external examination, there was significant hair loss in the occipital region, with remaining hair easily pulled out with little effort FIGURE 3 and FIGURE 10. White frothing edema fluid was emanating from her nares, and her lower extremities had pitting edema (both findings consistent with terminal heart failure). There were multiple blunt-force trauma injuries of varying ages over most body segments, including 2 distinct patterns of hand or foot impressions and 5 or 6 distinct belt buckle impressions. The legs had innumerable excoriations over the anterior bony prominences; both knees and both insteps had purulent ulcerations, with granulation tissue at their borders and new hemorrhage breaking through those scabs.

Internally, there was a clotting subdural hemorrhage (still bright red but not a flowing liquid), cerebral edema, multiple healing rib fractures, and a recently lacerated liver with hemoperitoneum (approximately 400 mL of dark blood-tinged fluid). The thymus was so minimal with such indistinct borders that it was barely recognized.

#### Microscopic Findings

Microscopically, there was abundant pulmonary edema and a markedly involuted thymus FIGURE 5E and FIGURE 5F. The myocardium had diffuse interstitial edema, small foci of hypertrophic myocytes, scattered foci of hypereosinophilic myocytes, and myocytes with contraction banding with and without visible necrosis FIGURE 6C, FIGURE 7E, and FIGURE 7F. Multiple myocytes and interstitial cells had an Anitschkow-type chromatin pattern FIGURE 9D, FIGURE 9E, and FIGURE 9F. Newborn blood spot screening was not performed. Toxicologic and microbiologic testing were noncontributory.

The cause of death was signed out as "Battered child syndrome with recent subdural hemorrhage, lacerated liver, and multiple old injuries."


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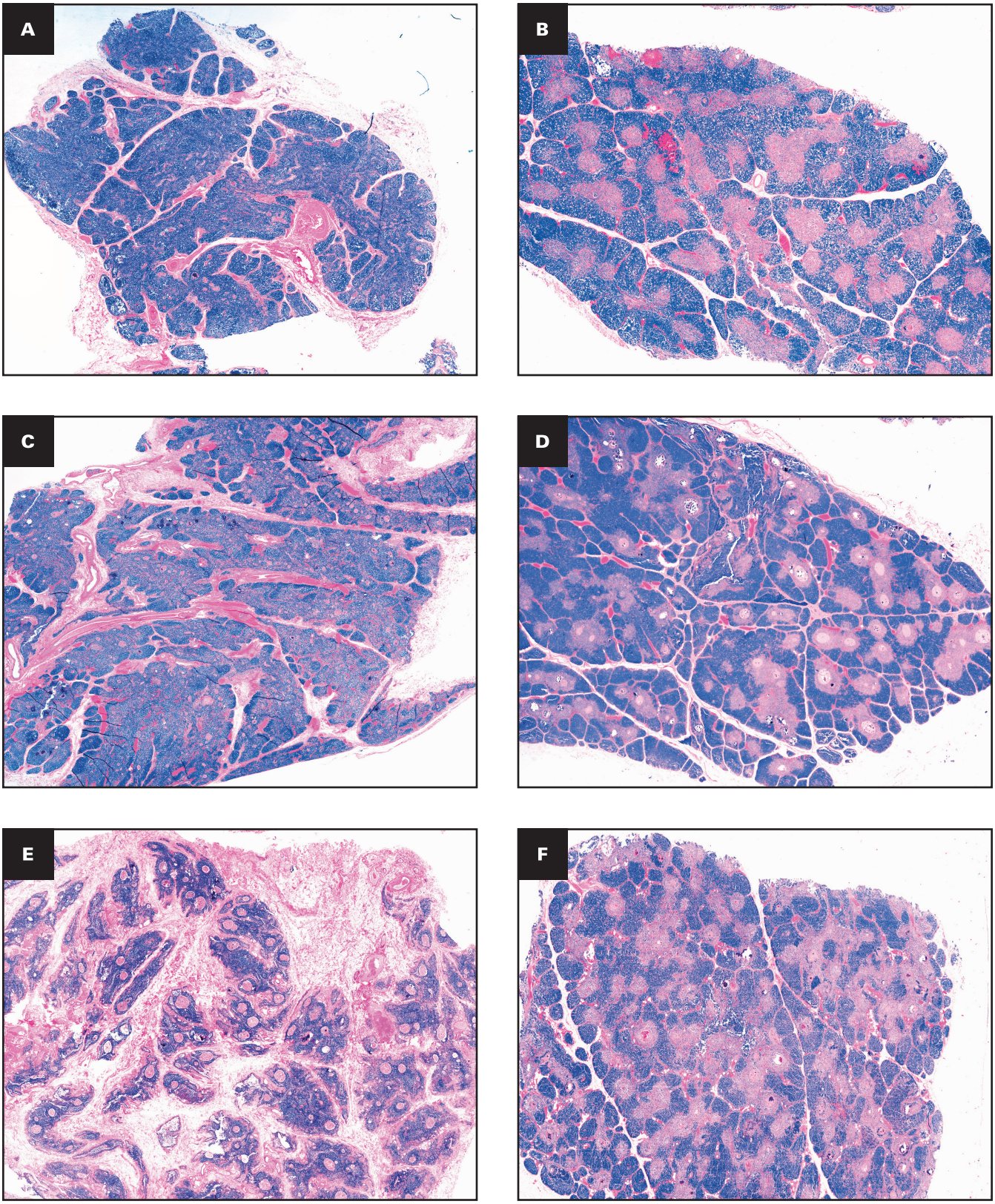


**FIGURE 5** Thymic involution of each case (**A**, **C**, **E**), with thymus of age-matched controls (**B**, **D**, **F**). (Glass microscope slides stained with H&E, all photographed with ×2.5 camera macro lens.)




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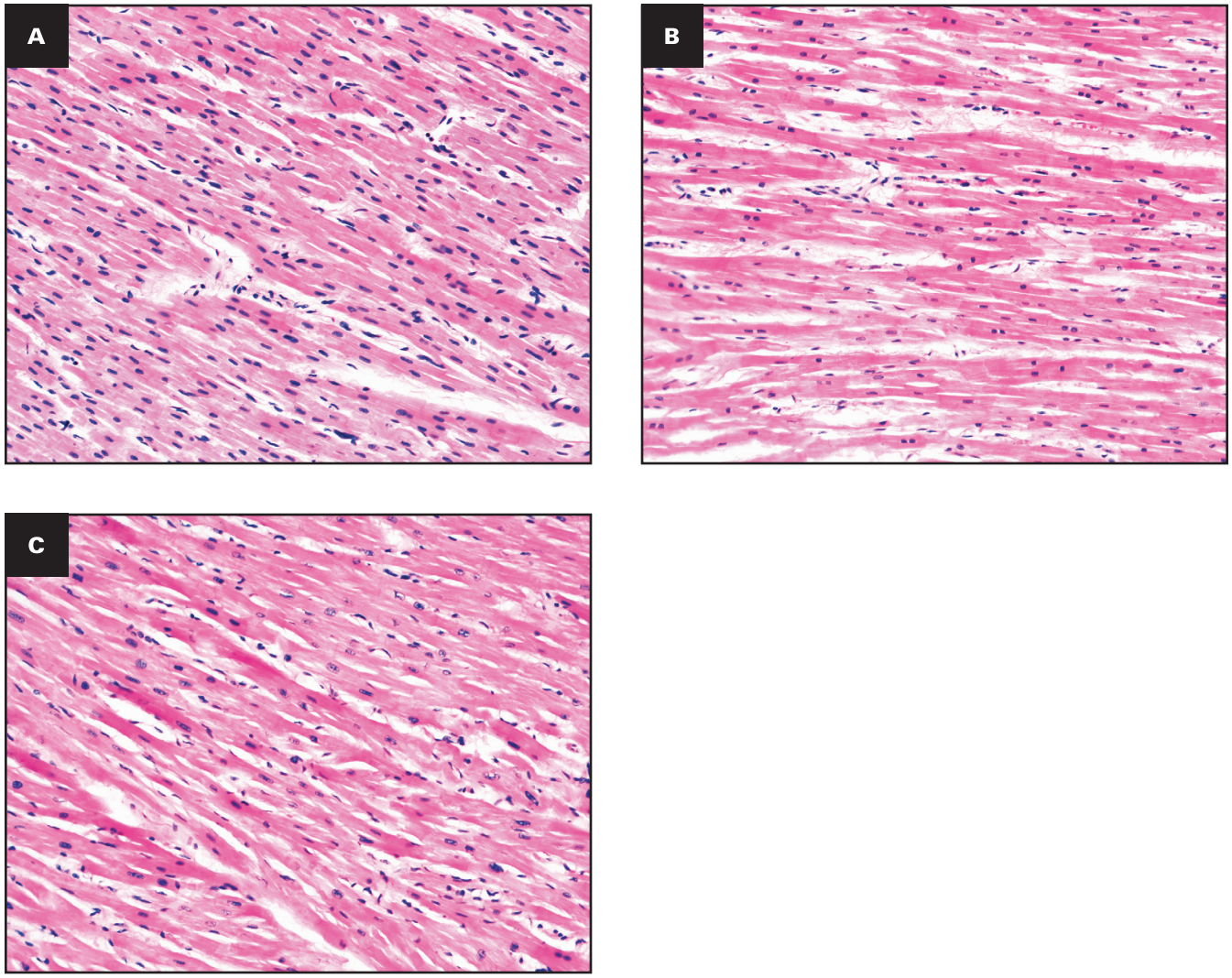


**FIGURE 6** Low-power views depicting myocardium with diffuse hypereosinophilia in 3 cases (H&E, ×10 objectives). **A**, Case 1; **B**, case 2; **C**, case 3.

## DISCUSSION

In medicine, stress is defined as a state of physiological or psychological strain caused by adverse stimuli—physical, mental, or emotional, internal or external—that tend to disturb the functioning of an organism and that the organism naturally desires to avoid. If the compensating reactions are inadequate or inappropriate, they may lead to disorders.[8] In severe acute stress, such as accompanies trauma or shock, the sympathetic nervous system is activated and catecholamines are released, leading to increased cardiac output, increased mean blood pressure, and a primed musculoskeletal system.[9]

In addition, the stress response includes triggering the adrenal cortex to release "stress hormones," such as cortisol. Because it is a precursor of the cortisol pathway, elevated levels of 17-OHP may represent elevated production of cortisol. It has been suggested that elevated levels of 17-OHP could be used as a clinical marker of stress of relatively long duration in neonates.[10]

The 2 younger girls in this study had blood spot genetic screening results for 17-OHP levels of 7.1 ng/mL and 10.8 ng/mL, respectively. For newborn screening purposes, anything greater than 4.0 ng/mL is considered abnormal (and may be worrisome for congenital adrenal hyperplasia).[11] In typical children, there should be a considerable drop in 17-OHP after the neonatal period; the published mean levels for typical 1- to 3-year-olds (comparable to case 1) should be approximately 0.20 ng/mL and for typical 3- to 5-year-olds (comparable to case 2) should be approximately 0.28 ng/mL.[12] In our cases, there were no indications of adrenal hyperplasia to otherwise account for these markedly elevated values, and we interpret these biochemical findings to be even further evidence of supraphysiologic stress.

We describe several findings that we propose are morphologic markers of either acute or chronic stress and may be indicators of child abuse or neglect. The hair loss in these 3 girls resulted from telogen effluvium, a known marker of chronic stress. The thymic involution in these 3 girls is also a known marker of chronic stress. The single-cell myocyte necrosis with contraction banding and hypereosinophilia are findings of catecholamine toxicity, which can be markers of acute stress. The Anitschkow-type chromatin patterns of myocardial cells are nonspecific markers of subacute or chronic cardiac


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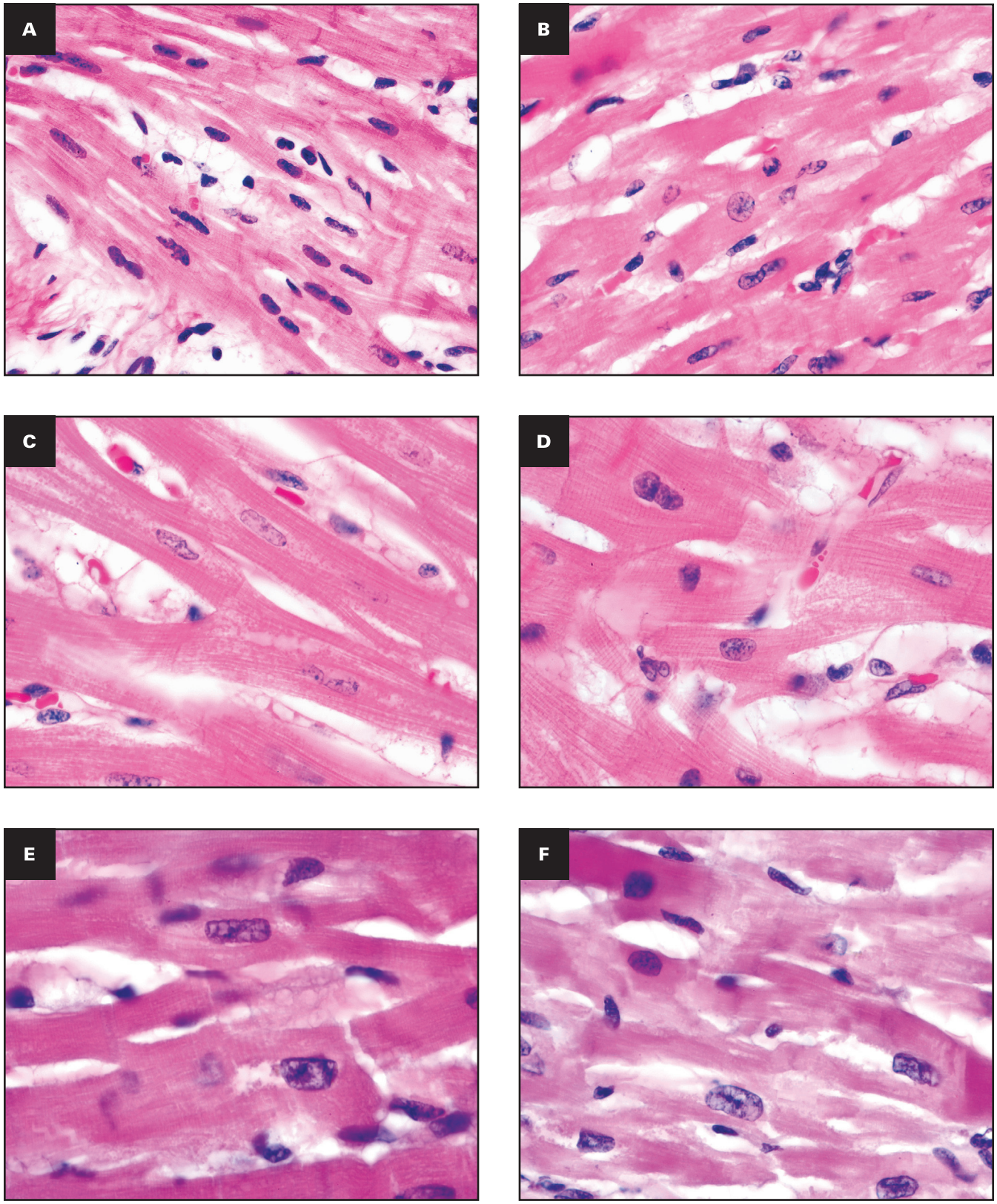


**FIGURE 7** Higher-power photomicrographs depicting myocyte catecholamine necrosis in 3 cases, including contraction banding, hypereosinophilia, myofibrillar disarray and dissolution, cytoplasmic vacuolization, and interstitial edema. **A**, Case 1; **B**, **C**, **D**, case 2; **E**, **F**, case 3. Cases 2 and 3 also demonstrate focal myocyte hypertrophy. (H&E; **A**, **B**, ×40 objectives; **C**, **D**, **E**, **F**, ×60 objectives).




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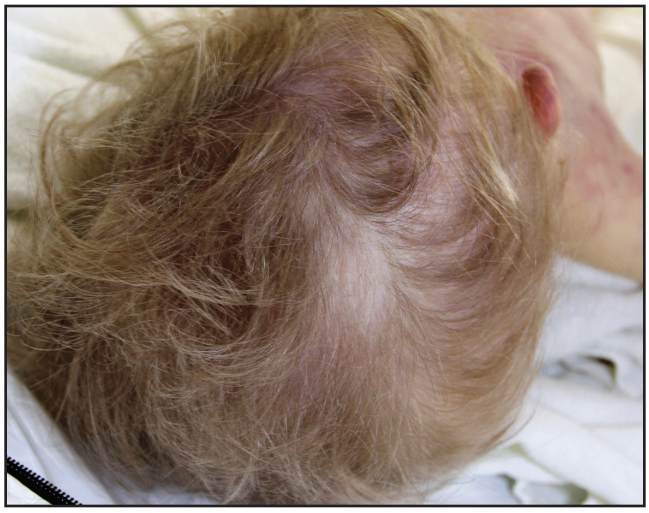

**FIGURE 8** Scalp of case 2.

pathologies, which are not typically evident in otherwise healthy or normal hearts; we propose that they may represent markers of stress from previous acute catecholamine toxicity. Each of these 4 topics is discussed below.

### Telogen Effluvium

Telogen effluvium is a form of diffuse alopecia in which an increased number of hairs prematurely enter the telogen phase and are shed in inappropriately large numbers, usually 1 to 3 months after a triggering event. The disorder may result as a reaction to a variety of physical, physiologic, or mental stressors, including major trauma, acute or chronic psychological stress (such as anxiety or depression), and emotional stress,[13-15] and is most often seen clinically in postpartum women.[16] The molecular mechanisms of development and regulation of hair follicles are being studied,[17,18] but the specific biochemical or hormonal pathways that cause telogen effluvium is still unknown. Although the condition is known in the pediatric population, those reports are usually described cursorily in the differential diagnosis of other forms of pediatric alopecia. There is virtually no reference to telogen effluvium in the forensic pathology literature.

Before this study, we had not commented on telogen effluvium or any other form of alopecia in autopsies of chronically abused children. It is possible that the condition may not have been there or may have been present in a much less dramatic form and so not noticed. When faced with overwhelming trauma, it is also likely that we did not consider this entity simply because it was not "on our radar." An additional (fourth) case was not investigated by our office but reviewed for consultation only. This case was a girl 3 years, 8 months old who had well-documented, chronic physical and psychological maltreatment; her cause of death was fatal child abuse. Our access to the file was markedly limited: Only social history, gross photographs, and the forensic pathologist's report were made available FIGURE 11 and FIGURE 12. The autopsy pathologist made no comments on the scalp finding that we believe is telogen effluvium.

Traumatic alopecia may grossly appear similar to telogen effluvium and should be in the differential diagnosis of nonscarring alopecia in children. Tight headbands, rubber bands, curlers, or similar traction devices can cause trauma to hair follicles. Trichotillomania, or hair pulling, will yield a similar outcome. In examining those scalps, gently pulling at the unaffected areas will yield minimal or no shed hairs. With telogen effluvium, however, much more of the remaining scalp hair will shed with gentle pulling.[19]

Although we did not look specifically at the hair bulbs in any of our cases, the gross and microscopic examination of the scalps revealed no other pathology, the simple hair-pulling tests was positive, and there was no prior report of traumatic etiologies.

We urge our colleagues to be aware of telogen effluvium. A visual inspection might be all that is necessary to pursue this diagnosis, if present. Gently pulling the hair may yield an excess of expected shed hairs. Those hair roots may be examined micro- or macroscopically for typical telogen (vs pulled anagen) follicles.[20] Histology of the scalp may also be helpful for ruling out other pathology.

Telogen effluvium would not be an expected finding if abuse is an acute event or had been occurring over several days. In adults, the condition typically does not manifest until 3 months after the initial triggering event. It is also a reversible condition and may require some element of constancy. In children, the timing of telogen effluvium may be more variable. Thymic involution may well be a more reliable and well-established marker of chronic stress, but if telogen effluvium is present, it will be visible while the child is still alive, and intervention by social services may be initiated to prevent this condition from ever becoming an autopsy finding.

### Thymic Involution

The thymus is a lymphoproliferative organ of multiple ill-defined lobules composed of lymphocytes and epithelial cells arranged into cortex and medulla whose delineations are appreciated only by the density of the lymphocytes. The cortex, with its much denser packing of lymphocytes, appears dark blue on standard H&E histologic preparations. The medulla, with its lower density of lymphocytes and more apparent stroma, appears more eosinophilic and often contains distinctive swirls of keratinizing epithelial cells known as Hassall bodies (or corpuscles). The morphology of the thymus reflects its immunologic functioning and is robust from fetal life through adolescence, and then begins to involute as part of the normal aging process, usually during the later teenage years. Normal hypoplasia or atrophic changes include a decrease in lymphoid elements and a gradual replacement by adipose tissue.[4,21]

Premature thymic hypoplasia with involution in children can occur as a result of stress from increased levels of corticosteroids.[22,23] Histologic parameters of thymic changes have been reported to be a reliable marker for acute illness before death.[24] Thymic involution in children is also reported in cases of persistent neglect and starvation.[25,26] The degree of thymic involution correlated well with the degree and period of maltreatment.[27]

The expected thymus weights in normal children for a 2.5-year-old is 34 g, for a 4-year-old is 35 g, and for a 10-year-old is 52 g.[28] The


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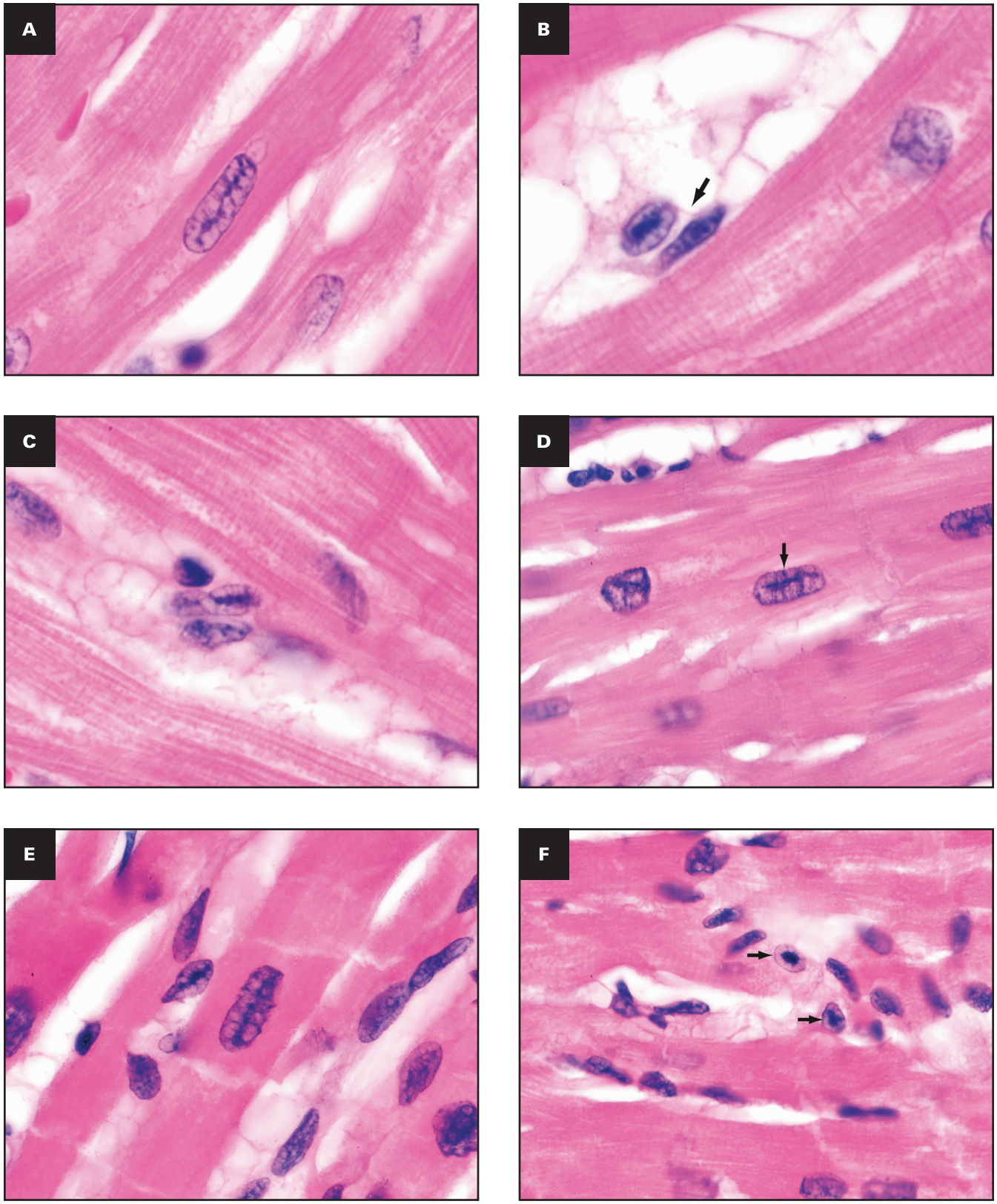


**FIGURE 9** Anitschkow-like chromatin patterns in myocardium from case 2 (**A**, **B**, **C**) and case 3 (**D**, **E**, **F**). **A-E**, Longitudinal sections display "caterpillar" pattern of nuclear chromatin, appearing to be of the myocytes. Slightly tangential sections of nuclei are in interstitial cells (arrows). **F**, Two transverse sections of nuclei display the "owl eye" pattern (arrows). (H&E, original objective magnifications ×60)




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thymic weights in the 3 cases presented here were 7.12 g, 13.0 g, and "barely recognizable," respectively.

FIGURE 5 shows the thymus glands of the three abused children on the left FIGURE 5A, FIGURE 5C, and FIGURE 5E next to thymus glands of closely age-matched children who died without history of abuse or chronic stress on the right (FIGURE 5B, FIGURE 5D, and FIGURE 5F, respectively). In all the "normals" FIGURE 5B, FIGURE 5D, and FIGURE 5F, there is a relatively sharp demarcation between the lymphocyte-rich blue cortex and the more eosinophilic medulla; in the 3 cases of abuse FIGURE 5A, FIGURE 5C, and FIGURE 5E, the demarcation is barely apparent if at all. Notice, too, that the lobular septa are much more prominent on the left because of either increased fibrosis or unmasking by a relative dearth of parenchyma. Thymic involution in case 3 FIGURE 5E is the most severe and likely correlates with the severity of the child's abuse; the pink circular elements surrounded by lymphocytes in that picture are Hassall corpuscles.

FIGURE 13 shows 2 examples of thymus in normal aging (physiologic involution) from otherwise healthy individuals. FIGURE 13A is a thymus from a 15-year-old: although the lobular stroma is becoming more apparent, the distinction between cortex and medulla is still well preserved. FIGURE 13B is a thymus from a 26-year-old: the lymphocytic population is markedly decreased, but the fibrous interstitium has appropriately transitioned to adipocytes.

The degree of thymic involution in our 3 cases clearly resulted from prolonged exposure to high levels of stress-related cortisol stimulation. Thymic involution should serve as a reliable indicator of chronic stress and may be significant autopsy evidence of prolonged abuse that can predate any visible soft-tissue trauma (with its relatively quick resolution).

Postmortem computed tomography (CT) imaging to evaluate thymus volumes before autopsy correlated well with the actual autopsy weights of those organs and made it possible to identify child maltreatment. The authors of that study concluded that this

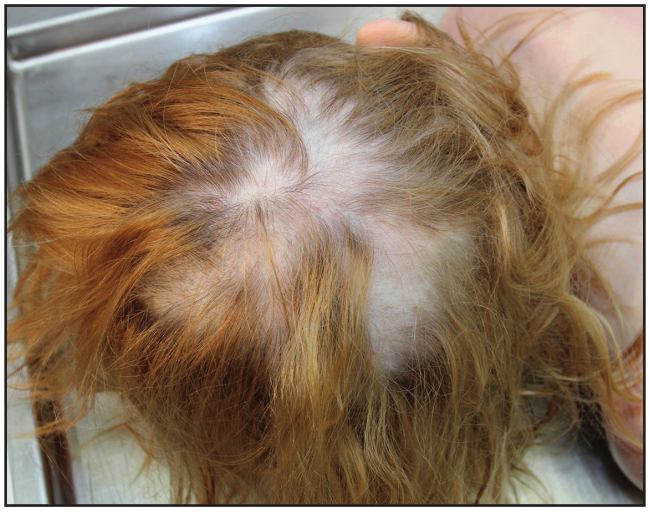

**FIGURE 10** Scalp of case 3.

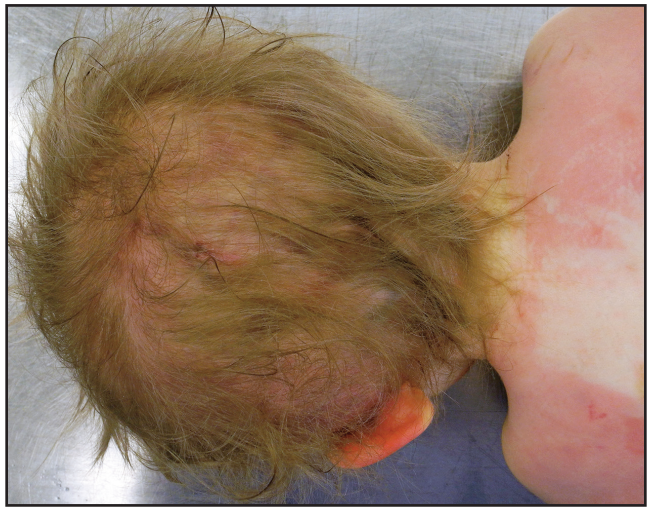

**FIGURE 12** Scalp of consult case.

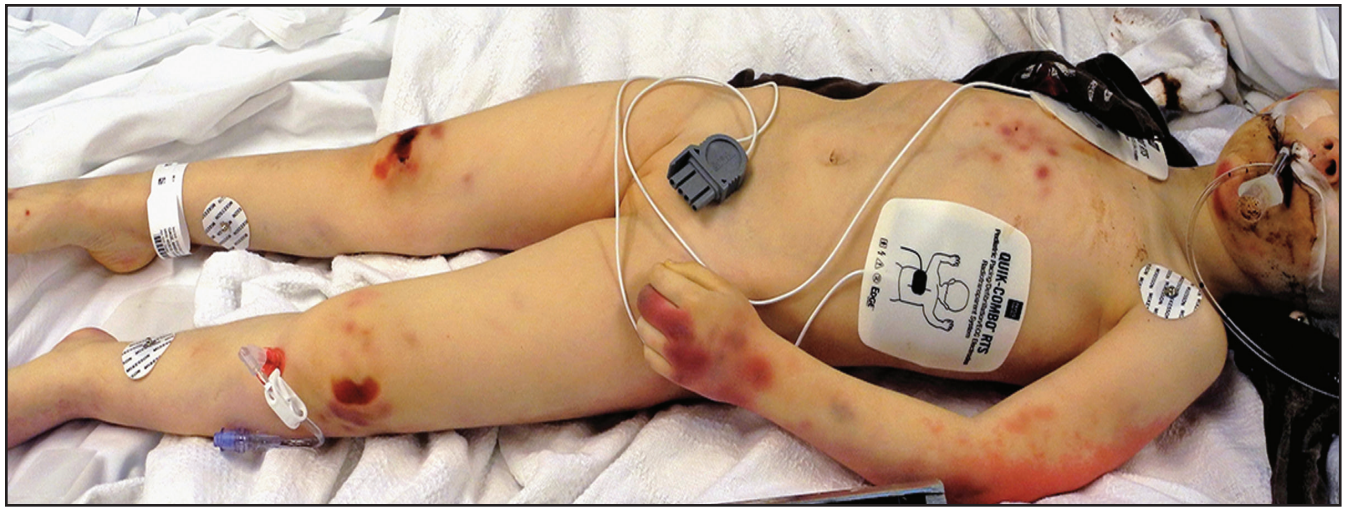


**FIGURE 11** Overall photo of consult case 3.75-year-old girl.


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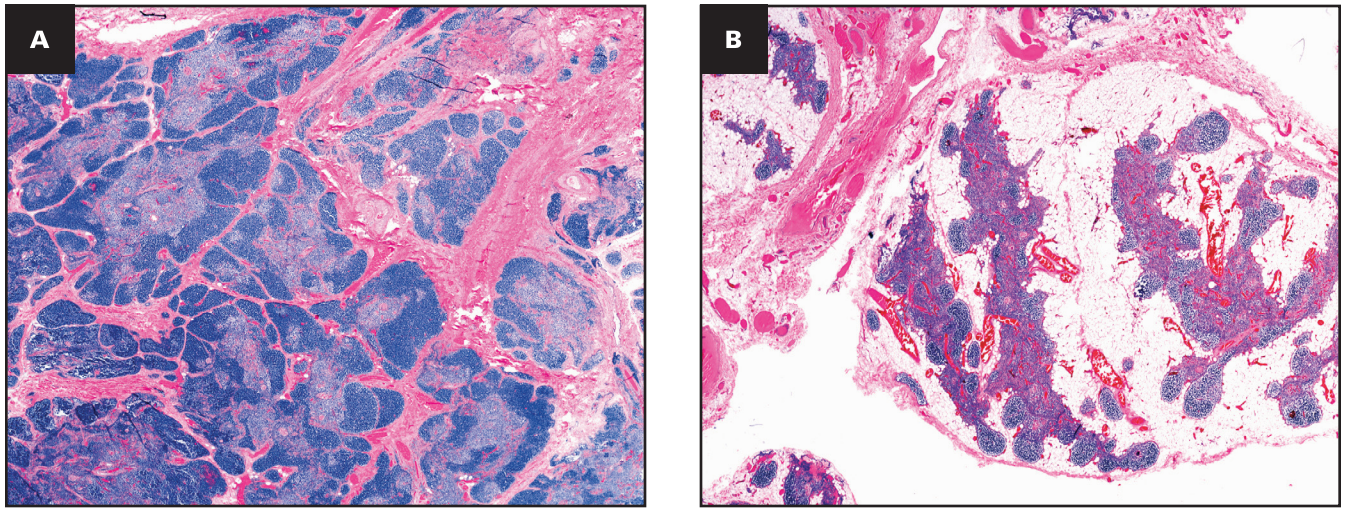


**FIGURE 13** Thymus of older patients depicting normal age-related involution. **A**, Well-preserved distinction between cortex and medulla despite overall decrease of parenchyma. **B**, Interstitium with fatty infiltration of septa. (Glass microscope slides stained with H&E, both with ×3.0 camera macro lens)

application of CT may be useful in demonstrating thymic involution in a surviving victim.[29]

### Catecholamines and Cardiotoxicity

The effects of catecholamine toxicity on the myocardium are well reported. Individuals with supraphysiologic levels of catecholamines—be they from exogenous sources, such as large amounts of pressor agents or cocaine, or endogenous pheochromocytoma—often have histologic findings nearly indistinguishable from those found in animal experiments where catecholamines were injected, including pulmonary edema, diffuse myocardial edema, alterations to myocardial nuclei, contraction band necrosis, and single-cell myocellular degeneration.[7,30-32]

The descriptors of myocyte death and necrosis may sometimes be confusing. The term coagulative necrosis refers to a pattern of cell death where the shape or form of the cell is still recognizable after death. This term is used mostly to distinguish that form of necrosis from other forms, such as liquefaction or caseous necroses, where the dead cells no longer maintain any resemblance to their noncytolyzed counterparts.[33] Because cardiac myocytes typically maintain their appearance after death, these cells are commonly described as undergoing coagulative (or sometimes coagulation) necrosis.

Myocardial cells, however, do not all die by the same mechanisms, and their histologic appearances may reflect those differences. In ischemic events, the myocytes die in the relaxation phase of the relaxation-contraction cycle, and their appearance after the first few hours of death may be virtually indistinguishable from their otherwise viable counterparts. It has been proposed that ischemia causes denaturation of both structural proteins and lytic enzymes, thereby preventing autolysis upon cell death.[33,34]

If myocytes die in the contraction phase of the relaxation-contraction cycle, especially from hypercontractility, they may display some characteristics that reflect that state, such as contraction banding and hypereosinophilia. The myocytes can also die while in a failing state and demonstrate progressive intracellular edema, with dissolution of myofibrils (sometimes referred to as colliquative myocytolysis).[35,36] The mechanism suggested is that excess levels of catecholamines (and their breakdown products) lead to increased permeability of the sarcolemma, causing an intracellular rush of $Ca^{2+}$.[7,37] This then causes an excessive opening of mitochondrial permeability transmembrane pores, resulting in lysis and structural degeneration of the myocytes[30] and causing intracellular edema and vacuolization.[35]

In all 3 of our cases, there was no indication of ischemia in myocytes, interstitium, or coronary arteries. FIGURE 6 and FIGURE 7 depict myocytolytic changes consistent with catecholamine cytotoxicity. In FIGURE 6 the diffuse nature of the hypereosinophilia is demonstrated (FIGURE 6A, FIGURE 6B, and FIGURE 6C for cases 1-3, respectively). FIGURE 7 provides higher-magnification photomicrographs of the same cases, depicting contraction banding, hypereosinophilia, myofibrillar disarray, myofibrillar dissolution, cytoplasmic vacuolization, and interstitial edema. FIGURE 7D, FIGURE 7E, and FIGURE 7F also show focal myocyte hypertrophy.

We posit that the molecular mechanisms described here may help explain our findings, where death was preceded by the immediate stress of actual or anticipated pain or the compromised functioning of organs from previous episodes of abuse. Supraphysiological catecholamine levels (in response to the stress) create excessive intracellular $Ca^{2+}$ concentrations, leading to increased contractility and cardiac dysfunction through direct stimulation of β1 receptors.[5] Excess catecholamine levels may also contribute a secondary insult: norepinephrine stimulation of α1- and β1-adrenergic receptors can cause smooth muscle contraction (vasoconstriction), increased heart rate, and increased myocardial contractility,[7] leading to a mismatch in the supply and demand of oxygen to the myocardium. Increased circulating catecholamines may also lead directly to coronary artery vasospasm.[38]




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Diffuse single-cell cardiac hypertrophy has also been reported in cases of catecholamine-induced myotoxicity.[39,40] If stress remains chronic, overstimulation of β2-adrenergic receptors leads to maladaptive cardiomyocyte hypertrophy, resulting in myocyte injury, dysfunction, and ultimately necrosis.[39]

In a study of 15 homicidal assaults, where complete autopsies disclosed no fatal internal trauma, 11 of the victims (73%) had cardiac changes consistent with "stress cardiomyopathy," with lesions comparable to those described in stressed animal experiments. The authors interpreted their data as supportive of the theory that stress-induced catecholamine release can mediate myocardial changes with lethal potential.[41]

In addition to the sudden cardiac deaths described in the above study, a more progressive decline of cardiac function from catecholamine toxicity can result in heart failure. Pulmonary edema observed in these cases are believed to result primarily from the heart failure, but direct catecholamine-induced pulmonary toxicity has also been cited as a contributory factor.[7]

### Anitschkow-Like Nuclear Changes in the Myocardium

On histologic examination of the myocardium of the older 2 girls (cases 2 and 3), we noted an abundance of cells whose nuclear chromatin patterns in longitudinal sections resembled caterpillars and in transverse section resembled owl eyes—the classic description of Anitschkow cells **FIGURE 9**.

In 1901, von Oppel described the reaction of rabbit myocardium 24 hours after traumatic disruption by a sewing needle. In addition to the obviously necrotic myocytes, there were cells slightly distant from the lesion with distinctive chromatin patterns ("serrated stripes") that were later described by Anitschkow after similar experiments and now bear his name. The pathognomonic lesion of rheumatic heart disease, the Aschoff body granuloma, classically contains Anitschkow cells.[42,43]

"Anitschkow cells" were later described in extracardiac locations and variously proposed to originate from cardiac myocytes, mononuclear histiocytes, or a host of other differentiated and undifferentiated cells.[44,45] This identical nuclear pattern has been described by veterinary pathologists in the hearts of stressed animals,[46] in the embryonic hearts of all vertebrates, and in the cardiomyocytes of immature infants.[47]

The current thinking is that there is no "Anitschkow cell" but only an "Anitschkow-like nuclear pattern," which may be found in various cell types, is a marker of cellular immaturity, and likely represents an attempt at cell division or—as here—an attempt at cardiac myocyte regeneration following injury.[47-49]

We propose that the presence of cells with Anitschkow-like nuclear patterns in the hearts of the 2 most severely abused children, without other cardiac pathology, likely represents nonspecific attempts at regeneration from injuries sustained during previous acute stress from catecholamine myocytolysis.

## CONCLUSIONS

We presented 3 cases of well-documented chronic maltreatment and neglect of children, aged 2.5, 4, and 10 years of age, who all died as a result of the acute and chronic stresses of abuse. Besides the abundant physical trauma, which may be loosely within the range of "acute," all 3 girls had pathologic markers of chronic abuse, as well.

The most commonly referenced finding related to chronic stress in children is an involuted thymus. Described mostly in the literature as resulting from chronic illness (or therapy), it is also known to be the result of other stressors, such as inflicted physical or psychological pain. The thymic involutions in our cases were absolutely consistent with and virtually diagnostic of chronic stress and without other underlying medical etiology.

All 3 of our cases had telogen effluvium, a known result of hormonal disturbances and chronic stress. Although occasionally described in the pediatric population, it has been mostly studied in adults. Certainly not every case of chronic stress will result in telogen effluvium as reliably as thymic involution; it may be more subtle or simply not present. We are not aware of other reports describing this condition in chronic child abuse. We are also cognizant of how "trivial" such an exam might appear to be when faced with the complex task of documenting the more substantial injuries, but as indicated with our additional consult case, it simply might be overlooked.

Catecholamine myocytolysis, an indicator of acute stress, was present in all 3 of our cases. This finding may be part of a prolonged dying process (for any reason); as cited earlier, however, it may also be the only finding when there is not enough physical trauma or disease to account for death.

Anitschkow-like chromatin patterns in the nuclei of heart cells were seen only in the 2 older victims (4 and 10 years of age). As discussed earlier, they likely represent a nonspecific reaction to injury or an attempt at regeneration. Without other underlying cardiac pathology, they—and the random hypertrophic myocyte—may be markers of previous catecholamine myocytolysis.

The term chronic child abuse syndrome is often applied as a cause of death when a child dies with multiple injuries on multiple dates and no one specific injury appears to be the fatal one. We presented this paper to make our colleagues aware of the constellation of findings that may be of use in documenting acute and chronic stress and its lethal potential.

Acknowledgments: We thank the entire staff of the Maine Office of Chief Medical Examiner, who assisted with the less-than-pleasant tasks of processing every aspect of these tragic cases.

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