A structural disaster: an undermining of underpinnings

For centuries memories of ancient quakes and volcanic destruction have permeated cultures residing in seismic lands. On Thursday morning, September 19, 1985, this century’s strongest earthquake struck Mexico; its epicenter lay 230 miles southwest of Mexico City, but the capital bore the brunt of its devastation. Thousands of lives were lost; human suffering was beyond description. Scaffolding, compromised by the initial shock, did not withstand the aftershock 36 h later – crumbled high rises became gravesites. Now one year later, plans were well underway to rehouse downtown residents – an in situ relocation plan for the most devastating site of destruction. New homes would feature traditional components: strong vivid colors; central patios; and a large common archway. Dr. Nick Fernandez, a serious-minded, recent graduate, had just joined the University of Mexico’s General Hospital to begin his residency in medicine. He marveled at the people’s resilience in overcoming this natural disaster. He recalled newspaper accounts of fallen rubble and found an inescapable analogy between this undermining of structural underpinnings and proteolytic digestion of extracellular matrix. Several newly acquired patients were noteworthy. Mr. S., a 42-year-old plumber with a long history of cigarette smoking and productive cough, now presented with dyspnea on exertion. In clinic, Nick found: S. leaning forward on the heels of his hands using accessory muscles with each inspiration and pursed lips during expiration; increased thoracic diameter, decreased diaphragmatic excursion, coarse basilar crackles and diminished breath sounds; radiographic evidence of overdistended lungs, especially at the bases; air flow obstruction, increased total lung and functional residual capacities, and diminished vital and carbon monoxide diffusing capacities on functional testing; and arterial hypoxemia without hypercapnia. Nick diagnosed emphysema due to homozygous $\alpha_1$ protease inhibitor deficiency — an inability to neutralize smoking-induced elastolytic activity in acinar tissue. Mrs. R., a 52-year-old librarian with bilateral symmetrical polyarthritis of hands and feet of 10 years duration, now complained of prolonged morning stiffness, poor grip strength and pain of involved joints that made lifting and sorting books difficult. Nick found fusiform swelling of proximal inter- (PIP) and metacarpophalangeal joints with hyperextension of PIP and flexion of distal IP joints. Elbows and wrists were now involved as well. Nick’s diagnosis was rheumatoid arthritis with progressive collagenolytic destruction of articular cartilage, ligaments and bone followed by fibrocontractive deformities. But what activates collagenase that normally resides in joint tissue in latent form? Mrs. G., a 42-year-old, gainfully employed gravida-5, para-4 accountant, now 2 months postpartum, was referred to Nick’s clinic. She noted the gradual appearance of dyspnea on exertion, orthopnea and weight gain following her recent uncomplicated pregnancy and delivery. There were no constitutional symptoms or viral prodrome. Biventricular dilatation with functional incompetence of mitral and tricuspid valves and ankle edema were found. Thin-walled, dilated right and left ventricles with systolic dysfunction were shown by echocardiography. Nick suspected peripartum cardiomyopathy. But why had this appeared in this otherwise healthy woman? Was this an immunologic reaction to uterine smooth muscle actin that crossreacted with contractile proteins of the myocardium? Why no vascular involvement? Alternatively, could this be a case of unbridled collagenolytic activity, involving the heart’s collagen matrix to promote ventricular dilatation and wall thinning with myocyte slippage?

Answer

Serine proteases, such as neutrophil elastase, are involved in the destruction of acinar elastin fibers. A deficiency of $\alpha_1$-protease inhibitor, a tissue protein that neu-
tralizes such proteolytic activity, accounts for unbridled elastin destruction leading to panacinar emphysema. An association exists between $\alpha_1$ antitrypsin deficiency and arteriopathy, including intracranial and abdominal aneurysms and cervical artery dissection. Invading inflammatory cells and macrophages contribute to destructive rheumatoid lesions. They release products that provoke collagenase production from fibroblast-like cells termed ‘synoviocytes’. Prostaglandin $E_2$ may be involved in this process in an autocrine/paracrine manner. Activation of this latent collagenase may be mediated by serine pro-teases, such as plasmin and trypsin, that are induced by plasminogen activators produced by endothelial cells of blood vessels formed as part of the inflammatory reaction (angiogenesis). Recent evidence indicates that collagenolytic activity is enhanced in the failing myopathic heart and could account for architectural and structural remodeling of chamber and tissue, respectively. Whether this is true for peripartum cardiomyopathy is unknown, as is the case for factors regulating collagenase activation in such hearts.