Yonsei Medical Journal
Vol. 43, No. 2, pp. 152 - 159, 2002

Original Article

Clinicopathologic Review of Pulmonary Silicone Embolism with Special Emphasis on the Resultant Histologic Diversity in the Lung - A Review of Five Cases -

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It is known that the subcutaneous injection of silicone can lead to severe pulmonary complications, followed in some patients by respiratory failure. Currently, silicone is being increasingly applied in the field of plastic surgery and, unfortunately, the illicit injection of silicone fluid by uncertified practitioners is not uncommon in Korea. We offer a critical pathologic review of 5 cases of pulmonary silicone embolism following illegal injection to the vaginal wall, four of which were fatal and came to legal autopsy. Our findings again confirm that subcutaneously injected silicone can gain access to the pulmonary vascular tree and cause pulmonary embolism. The histologic changes observed in the lung are variable and include four patterns i.e., the mere presence of silicone emboli, congestion and hemorrhage, acute pneumonitis, and diffuse alveolar damage despite the severe critical course in all cases. We were unable to find any histologic pattern that correlates well with the clinical course. Apart from producing emboli in the pulmonary vessels, subcutaneous injection of silicone can obviously cause serious pulmonary disease due to its ability to induce acute to induce acute pneumonitis and even possibly acute respiratory distress syndrome

Key Words: Silicone, pulmonary embolism, retrospective study, pathology

INTRODUCTION

The use of silicone fluid for medical purposes has been widespread, particularly for breast augmentaion and other cosmetic procedures. This substance (Polydimethylsiloxane) undergoes little if any change in physical properties and lacks immunogenicity, leading to its current wide application. However, animal studies with subcutaneously injected silicone have demonstrated that it can subsequently be recovered in various organs.[1,2] Indeed, there is a clinical case report[3] that bilateral silicone implants in one patient resulted in a severe systemic illness and there are also other reports that adverse effects including migration of the silicone,[4] granulomatous hepatitis[5] and an acute febrile systemic illness[6] resulted from illicit injections of silicone in humans. Nevertheless, only a few patients have been reported to have suffered acute systemic effects and subsequently died following silicone injection. In fact, pulmonary silicone embolism was only relatively recently reported as one of the possible systemic silicone complications.[7] In 1983, acute pneumonitis was first described to have occurred in three transsexual men following the subcutaneous injection of silicone.[7] There followed several other reports of pulmonary injury/pneumopathy associated with silicone injection.[8-18]

Serious complications of illicit silicone injection recently have come to the attention of pulmonary physicians in Korea, where only one fatal case had been previously reported[12]; that case is included in this study (case 3). We have sought to review our experience with four fatal and one surviving case of pulmonary embolism induced by the subcutaneous injection of silicone in order to eluci-

Received October 4, 2001
Accepted December 20, 2001

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date the morphologic spectrum displayed in the lung and determine if there is any possible predictor related to clinical evolution.

MATERIALS AND METHODS

All but one of the patients were identified from the database of the National Institute of Scientific Investigation. The other was from consultation files of one of the authors (D.H.S.). They were all adult females and previously in excellent health, with the exception of one who was later found at autopsy to have had inactivated pulmonary tuberculosis. Otherwise there were no preexisting disease or drug use known to induce pulmonary disease as evidenced from the legally authorized autopsy report. The authorized report also documented the interrelationship between illicit subcutaneous injection of silicone and the occurrence of the disease leading to death, with the exception of the surviving patient (case 4). In Case 4, the patient was hospitalized for symptoms presumed to be attributable to a previous silicone injection, which was later confirmed. Routine histologic sections from each lung were carefully reviewed and studied with additional histochemical stains including elastic tissue, trichrome, PAS and acid fast stain. In Case 1, infrared spectrophotometry was performed in order to clarify the nature of the material injected. In Case 5, the lung specimen fixed for scanning electron microscopy was washed, dehydrated with alcohol, and dried in CO_2 at the critical point. It was then sputter-coated with gold and observed with a scanning electron microscope (Hitachi S 800) at 20 kV. A retrospective clinical review was performed from charts submitted.

RESULTS

A variety of histopathologic changes were observed in the lung (Table 1). These included four patterns i.e., the mere presence of silicone emboli in two patients, and one each of congestion and hemorrhage, acute pneumonitis, and diffuse alveolar damage together with numerous silicone emboli.

CASE REPORTS

All patients received an illicit injection of an unknown volume of silicone in the vaginal wall administered by uncertified practitioners. One patient (case 1) received this injection into the breast and right shoulder as well.

Case 1

A 44-year-old woman was in stable condition until approximately 6 hours earlier when she began to complain of severe chest pain after receiving an illegal injection of silicone fluid into her breast, right shoulder, and vaginal wall. Upon admission, she was in comatose state with tachycardia and hypotension (60/40mmHg). A chest

Table 1. Clinicopathologic Summary of Five Cases

	Sex/Age	Onset of symptom after last injection	Previous silicone injection before last injection	Survival Duration	Pathologic findings
Case 1	F/44	6 hours	None	15 hours	silicone emboli only
Case 2	F/39	2 hours	1 week	10 hours	silicone emboli only
Case 3	F/32	less than 1 hour	12 days	5 days	edema, congestion & hemorrhage, extensive
Case 4	F/58	2 days	10 days	Alive	acute pneumonitis with hemorrhage
Case 5	F/46	2 days	None	31 days	diffuse alveolar damage & superimposed bacterial pneumonia

X-ray revealed extensive haziness in both lung fields. Despite intensive treatment, she expired just 15 hours after the silicone injection. At autpsy, there were numerous foci of subcutaneous hemorrhage and puncture sites for foreign material injections in both breasts, right shoulder, and the vaginal wall. The infra-red spectrophotometry revealed the foreign material to be silicone oil (Fig. 1). Microscopic examinations revealed variable sized lipid droplets in the alveolar capillaries not accompanied by any histologic abnormalities (Fig. 2).

Case 2

A 39-year-old woman presented with chest pain and disturbance of consciousness. She had separately received two illegal silicone fluid injections for so-called vaginoplasty 1 week and 2 hours before admission, respectively. A sudden onset of chest pain and disturbance of consciousness occurred during the second course of injection. Despite intensive treatment, she expired no more than 10 hours after the last silicone injection. At autopsy, silicone bags were found to have been inserted into both breasts. Both lungs were collapsed. Oil-like material was discovered to fill the vessel lumen. Microscopic examination revealed variable sized globular deposits in the alveolar capillaries. There was no acute inflammation and no granulomas were present.

Case 3

A32-year-old, previously healthy woman underwent a so-called vaginoplasty by a charlatan who infused silicone into the vaginal wall 12 days and again 5 days before admission. Sudden onset of loss of consciousness occurred during the second course of silicone fluid injection. She died of progressively worsening dyspnea 5 days after admission. At autopsy, a large amount of oil-like clear fluid freely exuded from the subcutaneous tissues of the labia majora. Both lungs showed marked

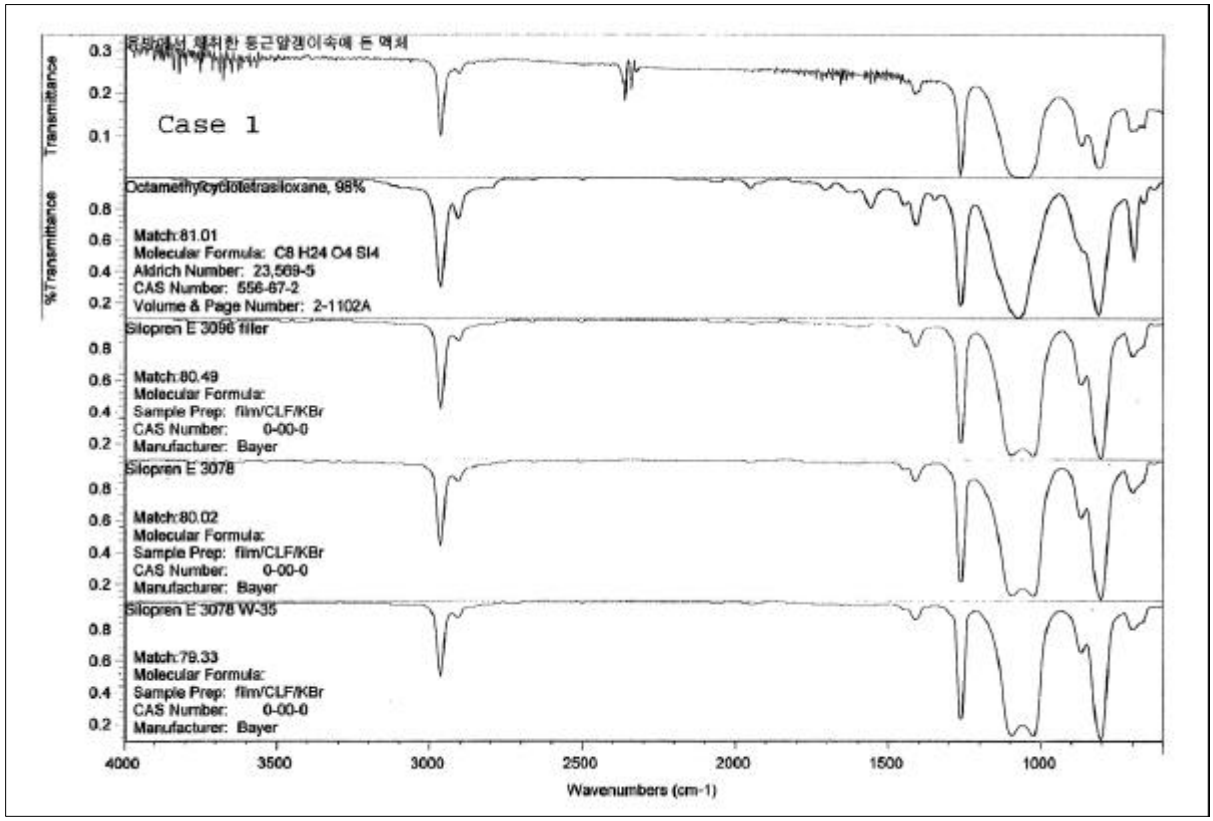

Fig. 1. Infrared spectrum corresponding to the liquid extracted and to the pattern (commercial methylsilicone). [FT-IR: magna-IR 560, Thermo Nicolet, Madison, WI, USA]

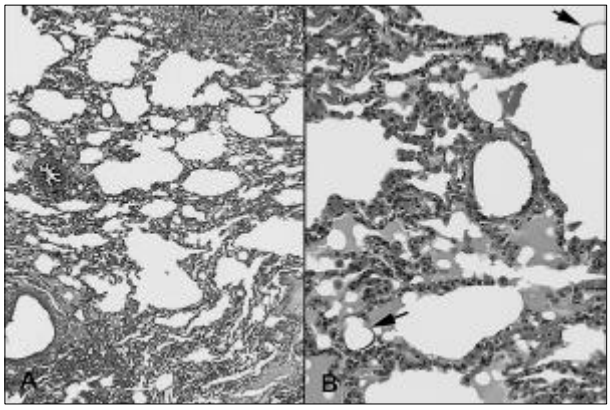

Fig. 2. Low power (A: × 40) and high power (B: × 200) view revealed variable sized lipid droplets in alveolar capillaries, not accompanied with any histologic abnormalities.

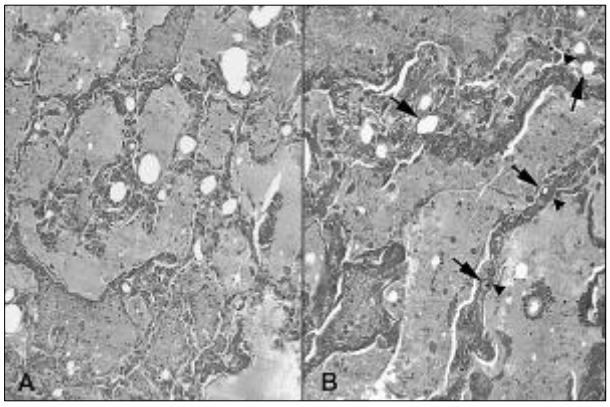

Fig. 3. Low power (A: × 100) and high power view (B: × 200) revealed no significant histologic changes other than congestion, alveolar hemorrhages and distended capillaries with variable sized globular vacuoles.

edema and extensive hemorrhage. Microscopic examinations of the lungs revealed no significant histologic changes other than congestion, alveolar hemorrhages and distended capillaries with variable sized globular vacuoles (Fig. 3).

Case 4

A 58-year-old woman was admitted because of fever, blood tinged sputum and dyspnea of two days. She had separately received two illegal silicone fluid injections into the buttock 10 days and 2 days before admission. Because of rapidly worsening dyspnea, an open lung biopsy was performed for diagnosis. Microscopic examination revealed marked embolism of a clear globular

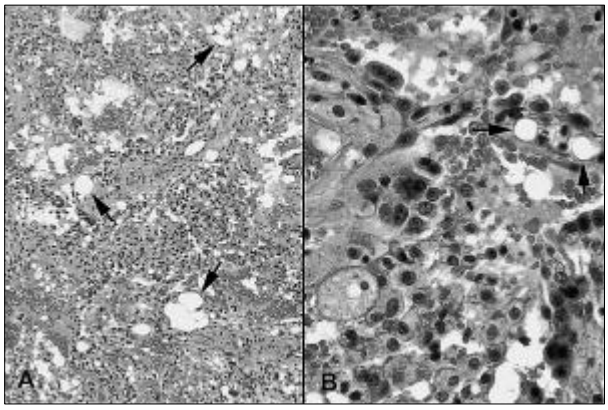

Fig. 4. High power view (B: × 400) revealed marked embolism of clear globular material, which had obstructed capillaries and many histiocytes, neutrophils, and lymphocytes in the alveolar spaces. Low power view (A: × 100) revealed edema, fibrin and hemorrhage suspected to be secondary to the marked vascular obstruction.

material, which had obstructed the capillaries. The material had extravasated into the alveoli, where it had become ingested by histiocytes. In the alveoli, there were many neutrophils and lymphocytes. Additionally, pulmonary edema, hemorrhage, and even pneumocyte atypia were seen but no hyaline membranes were detected. There was also edema, fibrin and hemorrhage suspected to be secondary to marked vascular obstruction (Fig. 4). We interpreted this lesion as silicone embolism with acute pneumonitis. She was transferred to another hospital for better evaluation and intensive treatment where she was discharged in stable condition after two weeks.

Case 5

A 46-year-old woman underwent a so-called vaginoplasty by a charlatan who infused silicone solution into the vaginal wall. She was said to have fallen into a state of shock about 10 minutes after infusion only to awake after a short while. She went home but two days later suddenly developed dyspnea and signs of nerve paralysis urging admission to one a university hospital where a clinical diagnosis of acute right heart failure due to pulmonary embolism was made based on the failure to further advance a Swan-Ganz catheter through the pulmonary artery from the right heart. She was treated empirically as such, but finally expired one month later. Premortem

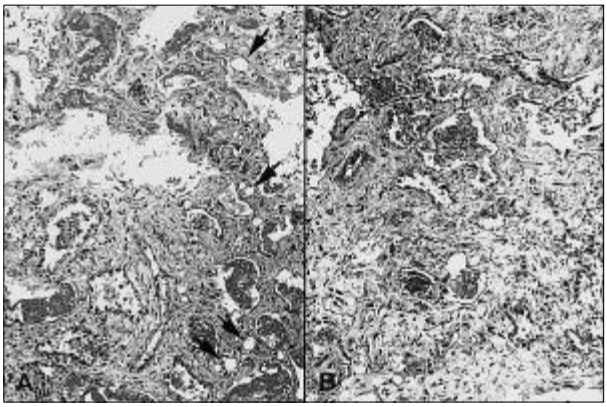

Fig. 5. Low power view (A, B: × 100) revealed acute and organizing diffuse alveolar damage with variable sized lipid droplets in the alveolar capillaries and interstitium.

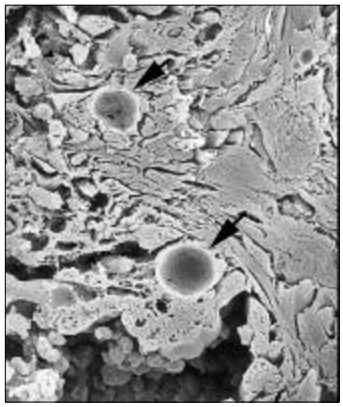

Fig. 6. Scanning electron microscopy demonstrated the nonstaining globular deposits to be silicone in the alveolar septal capillaries and within alveolar macrophages.

sputum stain revealed gram positive cocci, gram negative rods and acid-fast bacilli (2+). The throat culture exhibited a heavy growth of Klebsiella pneumonia. At autopsy, both lungs had increased consistency. Microscopic examination revealed acute and organizing diffuse alveolar damage. Variable sized lipid droplets were seen in the alveolar capillaries and interstitium with foreign body reaction (Fig. 5). Tuberculous granulomas were also seen and corticosteroids administered for acute lung injury may have predisposed the patients to reactivation of the tuberculosis. There was also pyogenic pneumonia that afflicted virtually the entire lung with tuberculous pneumonia. Scanning electron microscopy demonstrated the nonstaining globular deposits to be silicone in the alveolar septal capillaries and within the alveolar macrophages (Fig. 6).

DISCUSSION

The present study vividly shows that silicone can produce acute pulmonary disease in only a matter of hours after subcutaneous injection and that the silicone emboli were easily detected in the pulmonary vessels of patients who expired in as little as 10 hours following silicone injection. Thus it is clear that silicone injected into body tissue results in local tissue damage and eventually gains access to the bloodstream and embolizes to the lungs.

Silicone has long been used as a human biomaterial due to its excellent physical properties and lack of immunogenicity.[19] However local and systemic complication following silicone injection have been increasingly reported.[19-23] Local complications include infection, necrosis, and tissue reactions to foreign body.[19] Systemic complications include lymphadenopathy,[20] arthritis,[21] systemic foreign body reaction,[22] and connective tissue disease.[23] These complications are suspected to result from foreign body reactions and/or immune reactions. In 1975, Ellenbogen and coworkers[5] reported 4 cases of silicone injection complications including three cases of granulomatous hepatitis and one case of severe acute pulmonary edema and hemorrhage. Chastre and coworkers[7] described acute pneumonitis in three transsexual men following subcutaneous injection of silicone. They detected silicone in cells and supernatants obtained from the bronchoalveolar lavage and confirmed its presence by atomic absorption and infrared spectrophotometry. It was the first demonstration of injected silicone causing pulmonary embolism. In addition, they described two histologic forms of pneumopathy elicited by subcutaneous injections of silicone. An acute form usually occurs within days of the silicone injection whereas a latent form appears up to 6 months after the last injection. Afterwards, only anecdotal reports of silicone injection complications from cosmetic procedure, particularly illegally performed, appeared but finally it came to be known that even acute pneumonitis and acute respiratory distress syndrome could be induced by silicone

injection.[7-18]

Nonthrombotic pulmonary emboli are comparatively rare, although air or any type tissue or foreign material may enter into the vascular system and deposit in the pulmonary vascular tree. The pathogenesis of pulmonary disease caused by silicone is not clearly elucidated however it is strongly believed to be related to an embolization of the silicone and therefore the mechanism is suspected to be largely similar to that of pulmonary fat embolism,[7,10] since some additives or another oil may also contaminate the tissue at the time of illicit injection of silicone fluid.[13] Fat embolism is commonly associated with trauma, although nontraumatic fat embolism (i.e., burn, abdominal surgery, cardiac massage, diabetes mellitus) can also occur. It is not completely clear how fat embolism damages the lung but theoretically the deposition of fatty aggregates in small muscular arteries and arterioles can increase pulmonary artery pressures sufficiently to cause cor pulmonale given that the physiological and clinical impact heavily depends on the extent of the pulmonary vascular bed obliteration, the preexisting cardiopulmonary status of the patient and secondary effects that follow lodging of the emboli in the lungs.[24]

In the cases of the illegal practice of silicone injection, the mechanism of pulmonary silicone embolism may be complicated and perhaps related to high local tissue pressure induced by large-dose and high-pressure injection, local massage by the illegal practitioner, migration effect, or direct intravascular injections.[3,5,7,11] Two of our patients (case 1 and 2) expired only 10 hours or slightly longer after the last silicone injection. The amount of injected silicone fluid was not known in the cases of illicit injection by an uncertified practitioner, however the injection may have been greater than usual because one patient (case 1) received multiple injections into the breast, shoulder and vaginal wall as well, and in another patient an oil-like material was readily noted to have filled the pulmonary vessel lumen at autopsy. Therefore it is strongly possible that the sheer amount of injected silicone could obliterate the pulmonary vascular bed sufficiently to evoke acute cor pulmonale and finally death, however it is not certain why there were no associated histologic changes despite the interval after the previous injection in Case 2. In Cases 3 and 4, there was only extensive hemorrhage in addition to the intravascular globular emboli. The reason for extensive hemorrhage can be explained simply by an obstruction of the vascular bed by numerous emboli, although it is also possible that a capillary leak syndrome may occur as in a fat embolism, presumably due to lysis of the fatty aggregates by lung lipases to form free fatty acids. It is noteworthy that thrombocytopenia and the resultant petechiae occur in fat embolism syndrome, possibly secondarily to platelet aggregation by the circulating fat.[24]

Acute pneumonitis was encountered in only one patient (case 4). The acute pneumonitis consists of many neutrophils, lymphocytes and macrophages ingesting silicone, as well as edema and hemorrhage but without a hyaline membrane. The hemorrhage observed in the alveoli obviously accounted for the blood-tinged sputum. The acute pneumonitis may be induced by a spillage of silicone fluid into the alveolar space, however the influx of neutrophils, eosinophils and alveolar macrophages in the fluid taken from the bronchalveolar lavage can account for the fact that localized cell-mediated inflammation may play an important role in the pathogenesis of silicone embolism.[10] In fact the patient (case 4) had received a similar injection prior to the last injection, so there was an interval within which acute pneumonitis could possibly develop supporting cell-mediated inflammation.

Goldblum and coworkers[25] first demonstrated the presence of an antibody to silicone in serum. Furthermore, Narini and coworkers[26] suggested that repeated exposure to silicone gel can induce delayed hypersensitivity and thus it was suggested that an immunologic mechanism may have a role in pulmonary silicone embolism. If an immunologic mechanism is at work, this may explain at least partly why pulmonary silicone embolism usually occurs after more than one injection in most patients.[13] This is in accordance with the previous history of injection in three of five patients in the present study.

All five cases of pulmonary embolism described herein were induced by illicit silicone injection to the vaginal wall, as were the other cases

previously reported in Korea.[12,17] Most of the reported cases in Western countries are notably different from the reports from Korea in that all occurred in patients receiving illicit silicone injection into subcutaneous tissues for mammoplasty. It seems partly because large volume of silicone is more likely to be used in te augmentation mammaplasty and injection to the vaginal wall is still prevalently performed by uncertified practitioners.

Our patients appeared to have followed a similar clinical course: an acute onset of dyspnea on exertion associated with chest pain, blood-tinged sputum and mild fever. Moderate to severe hypoxemia was also seen. Histologic examination showed distended pulmonary capillaries filled with a homogenous, nonstainable clear globular material later identified as silicone in all cases. The associated pathologic findings were variable ranging from the mere presence of silicone emboli within pulmonary vessels, congestion and hemorrhage, as well as acute pneumonitis to diffuse alveolar damage. We suspect that this variety of histologic changes depends on a complex interplay between the degree of mounted cellular mediated inflammation, host individuality and the amount of injected silicone. In the two fatal cases with only a short interval between symptom onset and death, there were only minimal pathologic findings. It is possible that some patients may suffer from acute cor pulmonale caused by a relatively large amount of silicone and hence the resultant pathologic finding was minimal as seen in Case 1 and 2. In contrast, the most severe pathologic findings, i.e., diffuse alveolar damage, occured in Case 5 who had survived for as long as 31 days. Although it may be argued that the diffuse alveolar damage was secondary to ventilator therapy because the patient was on a ventilator during much of the admission period, it is certainly conceivable that the patient developed diffuse alveolar damage secondary to an initial episode of hypotension as well as an apparently major pulmonary embolism. However, it can not be definitively determined whether pulmonary silicone embolism can lead to ARDS/diffuse alveolar damage by its own right or if the diffuse alveolar damage found in the lung at autopsy represents the effects of ventilator therapy. In the patients studied, there was no latent form as described by Ellenbogen and coworkers,[5] because we dealt with acute serious cases. In Korea, illicit injections of silicone fluid are performed with such frequency that all physicians should be alert to the possibility of silicone toxicity in patients with a history of subcutaneous injection because the chronic release of small amounts of silicone from a subcutaneous depot can gain access to blood stream as suggested.[10]

There are a few weaknesses in this study. First, the number of cases studied is so small in number that it is hard for this study to have encompassed the entire spectrum of histologic patterns deriving from silicone embolism. Second, we can not exclude the possibility of other factors affecting the clinicopathologic results, particularly of the legal autopsy cases because the patients were given an illicit injection of an unknown volume by an uncertified practitioner and the clinical course was so rapid that a complete medical evaluation in terms of a biologic study could not be carried out in each case.

In summary, it is clear that silicone injected subcutaneously gained access to the vascular system and then lodged in the pulmonary vessels causing acute pulmonary diseases. Four patients expired. A variety of pathologic changes occurred which were acute and consisted of the mere presence of intravascular silicone emboli, extensive edema and hemorrhage, acute pneumonitis and even diffuse alveolar damage. How these variable histologic changes can be induced by simple subcutaneous injection of silicone remains to be investigated. In view of the frequency of illicit injections of silicone still being performed and the potential for pulmonary toxicity, a close follow-up should be maintained in any asymptomatic persons with silicone injection.

ACKNOWLEDGMENTS

The authors thank Drs Eugene Mark and Anna-Luise Katzenstein for their critical microscopic review of Cases 4 and 5. The authors also thank Yoon Jung Choi, M.D. Kyu Rae Kim, M.D. and Gap Rae Jo, M.D. for referring material and assisting in the work up of their cases.

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