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Human Pulmonary Histopathological Changes from Marijuana Smoking

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ABSTRACT: Thirteen individuals ranging in age from fifteen to forty years, who were known smokers of marijuana, all of whom died suddenly, were autopsied as coroner's cases. The pulmonary histopathologic changes revealed light to heavy infiltrations of pigmented monocytes within alveoli as well as varying degrees of monocytic and lymphocytic infiltration into the interstitium of the lungs. The intensity of the pulmonary infiltrate appears to be dose related. This report calls attention to the accelerated pathological changes in the lungs from marijuana smoking as compared to tobacco smoking leading to pulmonary scarring, emphysema, and eventual chronic obstructive pulmonary disease.

KEYWORDS: toxicology, pathology and biology, marijuana, pigmented macrophages, squamous metaplasia, lymphocytes, alveoli, bronchioles, bronchi, interestitial tissues, columnar epithelium, pulmonary fibrosis

The effects of marijuana smoking have been extensively documented in animal models by controlled inhalation of marijuana and tobacco smoke [*1,2*]. Histopathological lung changes from marijuana smoking in live humans have been obtained by bronchial biopsies and saline pulmonary lavage for cells within the alveoli [*3,4*]. There are limited autopsied histopathological studies on lung changes in humans who have smoked marijuana, so it is the purpose of this article to present histopathological findings involving the lungs of 13 individuals ranging in age from 15 to 40 years, all of whom died suddenly and violently except for Case 210, who died of a drug overdose (Table 1). At autopsy all of the cases were free of cardiac or infectious pulmonary disease or malignancy that could account for any pulmonary pathological changes which would interfere with the findings in this report. All of these individuals were known users of marijuana by history and eight cases also have a positive EMIT® (semiquantative enzyme immunoassay of cannabinoids—Syva Co.) urine test. Because of the circumstances involving these cases it is not possible to get a detailed history of the extent of the use of marijuana, tobacco, or drugs in general, but in obtaining information about all of these cases, such responses as "heavy user of marijuana" or "known user of marijuana" were given by friends or acquaintances.

Findings

In each case random sections of lung tissue taken for histological examination showed a great increase of pigmented macrophages within the alveoli. The pigment ranged from a light to a heavy brown with H & E staining, and it is distinguishable from anthracotic pigment

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TABLE 1—*Pertinent information about cases presented.*

Case	Age	Sex	Cause of Death	Urine Cannabinoids	Lung Macrophage Pattern	Macrophage
10	28	M	shot in chest	present	focal	2 Plus
11	30	M	shot in body	present	focal	1 Plus
31	38	F	strangulation	not done	focal	1 Plus
50	41	M	stabbing	present	focal	2 Plus
94	26	F	shot in chest	not done	focal	2 Plus
98	24	M	stabbing	not done	focal	2 Plus
126	38	F	car accident	present	diffuse	3 Plus
127	32	M	shot in chest	not done	diffuse	4 Plus
138	28	M	shot in chest	not done	diffuse	4 Plus
178	15	M	asphyxia	present	focal	2 Plus
180	29	M	car accident	present	diffuse	2 Plus
210	32	M	drug overdose	present	focal	1 Plus
225	27	M	car accident	present	focal	1 Plus

"EMIT—d.a.u. Semiquantitative Enzyme Immunoassay of Cannabinoids in Urine—Syva Co.

commonly found in lungs. The macrophages in all of the cases were stained for iron, and Cases 178 and 180 were stained for the presence of melanin. The stains were negative for iron and melanin.

Under microscopic low power the infiltrate can be divided into two general categories.

1. Focal, with most of the alveoli containing macrophages that are located about small bronchi while the more peripheral alveoli are relatively free of cells.

2. The diffuse infiltrate, which forms an even pattern of macrophages infiltrating the air sacs for a considerable distance from the bronchioles, resulting in a confluent picture. It is interesting that in nearly all of the cases that have sections taken from the periphery of the lungs, many focal collections of macrophages are in air sacs next to the visceral pleura.

In both focal and diffuse infiltrates of macrophages there is relatively little lymphocytes response although in the areas where small bronchi, bronchioles, and vessels are together they are frequently present. Where the infiltrate of macrophages are heavy and largely fill alveolar spaces there is usually a proliferation of fibrous tissue in the septal walls with some lymphocytic response indicating that the products of combustion of marijuana smoking are mildly irritating to the lung. In Case 138, a known "heavy user of marijuana" who was dyspneic on exertion before being shot, has most of his alveoli filled with pigmented macrophages in many parts of the lungs (Fig. 1). Focal areas of fibrosis are noted within the alveolar walls and about small bronchi. These areas of tissue scarring appear to result from the heavy infiltrate of macrophages, but early pulmonary fibrosis as a result of a combination of marijuana and years of cigarette smoking cannot be ruled out.

Critical examination for fibrosis in response to marijuana smoking shows slight to moderate changes in all of the cases in this series. Those cases in this study that have a lighter infiltrate of macrophages may indicate a dose relationship from a limited use of marijuana. The opposite is true in those with a known history of "heavy use" of marijuana where fibrosis is evident. There is a tendency in cases that have a heavy infiltrate for some pigmented macrophages to migrate into interstitial tissues, especially adjacent to bronchi. Here again there is some fibrous tissue response that is relatively minimal, except in those cases that have a heavy infiltrate of macrophages along with lymphocytes (Fig. 2).

In nearly all cases there is evidence of ulceration of the columnar mucosal epithelium of small bronchi, especially if large numbers of macrophages are present within the lumina of the bronchi. These areas of ulcerations are scattered throughout the lungs and in all cases

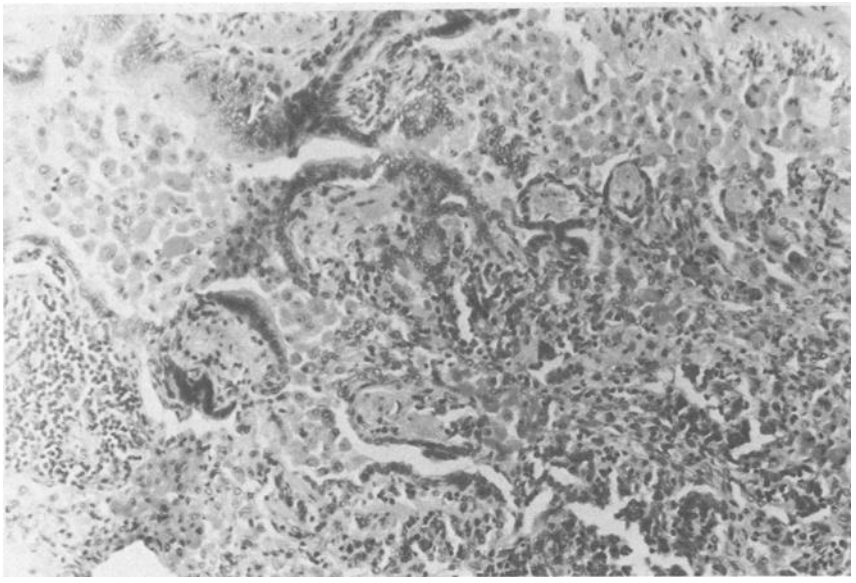

FIG. 1—*Twenty-eight-year-old male (Case 138), heavy infiltration of pigmented macrophages within a small bronchus, in surrounding alveoli, within the interstitium of the lung along with lymphocytes (×120).*

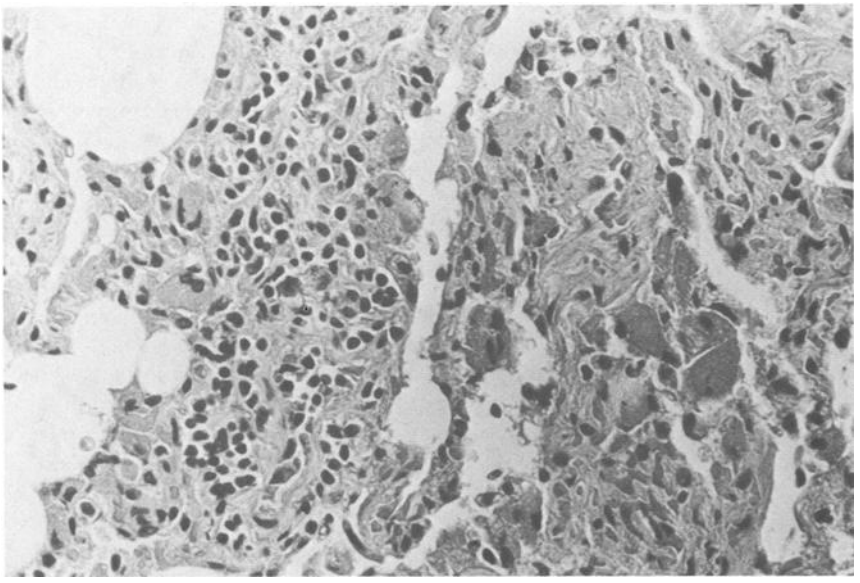

FIG. 2—*Thirty-two-year-old male (Case 127), many pigmented macrophages and lymphocytes within a proliferation of scar tissue in the lung (×300).*

ulceration probably will be found if enough sections are examined. Often ulceration is located in the terminal bronchioles just before the cuboidal epithelial cells are replaced by the alveolar Type I epithelium. When larger bronchioles are ulcerated there usually are a few chronic inflammatory cells present in the underlying submucosa and muscular stroma. Medium-sized and larger bronchi are occasionally found in some sections, but the columnar epithelium of

many generally are not well preserved because of postmortem changes. In this study those larger bronchi which have well-preserved columnar epithelium show no ulceration or squamous metaplasia.

Discussion

The single most characteristic finding in this study is the presence of large numbers of pigmented macrophages within the alveoli of the lungs. The patchy versus the diffuse infiltrate probably is dose related, although this cannot be proved. The numbers of macrophages present in the lungs is likely related to the frequency and length of time the subject has been smoking [1].

Case 138, a know heavy user, had dyspnea on exertion shortly before being shot. His lungs are heavily infiltrated, in most regions examined, where a large number of alveoli are completely filled with pigmented macrophages. It is also noted that the interstitial tissues, especially about bronchioles, are extensively infiltrated with macrophages along with many lymphocytes. Interstitial fibrosis is present in areas most heavily involved.

In all of the cases squamous metaplasia is rarely noted in small and terminal bronchi since the injury to the columnar epithelium is acute enough to cause ulceration of the mucosa rather than responding to prolonged irritation by undergoing squamous metaplasia.

Since marijuana has poor combustibility, it has up to 50% more polyaromatic hydrocarbons in its smoke than tobacco has [5] and the smoke also has more tar, cannabinoids, sterols, and other compounds that are irritating to the lungs [6, 7]. Since marijuana smokers usually deeply inhale smoke to get a maximum physiological response, it results in a deposit of particles of poorly burned products out to the periphery of the lungs in nearly all cases. Macrophages are called out in large numbers to phagocytize the foreign particles inhaled into the lungs. In a recent paper it has been pointed out that there are many macrophages located on the surface of the alveolar epithelium as well as macrophages in the interstitium and capillaries of the lungs. In response to injury if more macrophages are needed they are readily supplied by migration into the air sac from these reservoirs [8]. The irritants in marijuana smoke elicit macrophages as a response to injury in far greater magnitude than tobacco smoke does.

Lungs of tobacco smokers in this age group, dying under similar circumstances, show little or no significant macrophage response to tobacco smoke, although it is occasionally possible in very heavy tobacco-only smokers of long standing to have a few to moderate numbers of macrophages in the alveoli throughout the lungs, as found in a recent autopsy at our office. Tobacco smoking generally elicits a minimal number of macrophages in response to injury. Lung changes from tobacco smoking alone require exposure of many years to develop comparable fibrosis and inflammatory changes found in marijuana smokers. It has been pointed out that marijuana and tobacco smoking together hasten clinical symptoms and histopathological changes characterized by interstitial fibrosis. This is likely if smoking is continued over a period of years. Marijuana smoking alone causes significant pulmonary changes faster than tobacco smoking alone [3, 5, 7].

Case 178, a fifteen-year-old boy who died by asphyxia, had smoked marijuana for two years. As far as can be determined he did not smoke tobacco. It is impressive to see the extensive focal infiltrate of heavily pigmented macrophages within and about bronchioles, with focal ulceration of the columnar epithelium of many of the bronchioles, focal early fibrosis with lymphocytes and the presence of macrophages (Fig. 3). In this case, as in most cases, macrophages are focally deposited in the periphery of the lungs.

Marijuana smoking is much more injurious to the lungs than tobacco smoking as illustrated in the case of the 15-year-old boy. In two years of marijuana smoking more injury is present in his lungs than is found in people smoking tobacco over many years. One wonders what the prolonged effects of marijuana (together with tobacco) smoking will have on users in years to come. There probably will be a higher incidence of chronic obstructive pulmonary

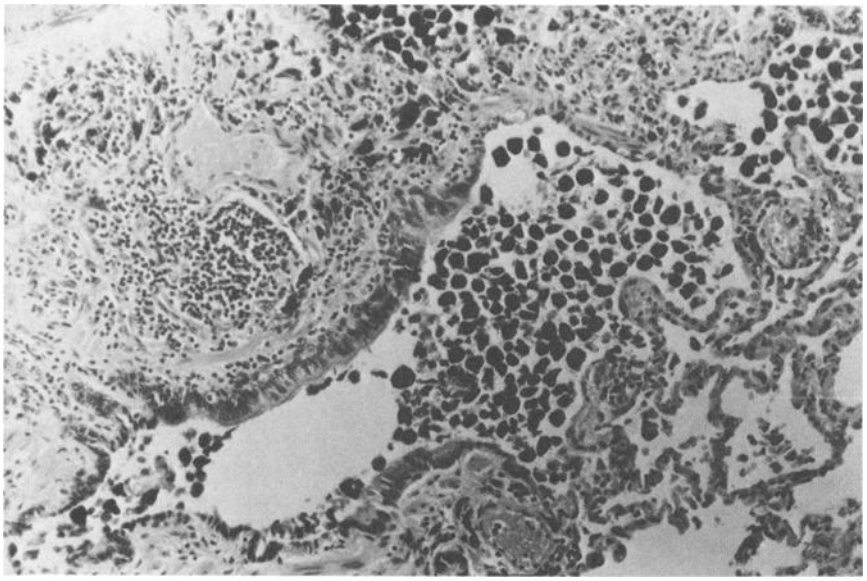

FIG. 3—*Fifteen-year-old male (Case 178), small bronchus with partial ulceration of the columnar epithelial lining and a large number of dark brown macrophages are in the lumen, in the adjacent alveoli, and a few are in the interstitial tissues along with lymphocytes (×120).*

disease and lung cancer. It is hoped that this report will stimulate a greater number of autopsy examinations on known marijuana smokers in order to accumulate more knowledge of the pathological findings for this type of smoking.

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