REVIEW

Lymphocytic interstitial pneumonitis in HIV infected adults

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Objectives: To describe current knowledge on the aetiology, pathology, presentation, diagnosis, and treatment of lymphocytic interstitial pneumonitis in HIV infected adults.
Methods: A Medline search was performed using the key words "HIV," "pneumonitis," and "lymphocytes." A further search was performed with the MESH heading "interstitial lung disorders." Related articles were also searched using Pubmed.
Results: Lymphocytic interstitial pneumonitis is a common complication in HIV infected children. In adults it is uncommon and is described most commonly among black African and Afro-Caribbean patients. The aetiology and pathogenesis of lymphocytic interstitial pneumonitis in HIV infection is not clear. The clinical and radiological presentations may be indistinguishable from *Pneumocystis carinii* infection and a lung biopsy is necessary to establish the diagnosis. Recent evidence suggests that lymphocytic interstitial pneumonitis in HIV infected patients may respond to combination antiretroviral therapy with dramatic improvements in clinical and radiological abnormalities.
Conclusion: Lymphocytic interstitial pneumonitis in HIV infected patients is a treatable condition. This condition should be considered in HIV infected patients presenting with respiratory symptoms as they may gain considerable benefit from antiretroviral therapy.

Infection and malignancy are common causes of interstitial lung disorders in HIV infected individuals. However, some HIV infected patients develop symptomatic non-infectious inflammatory interstitial lung disease. At one end of the spectrum is non-specific interstitial pneumonitis, which is common in adults, and at the other end is lymphocytic interstitial pneumonitis, which is common in children and less frequently described in HIV infected adults.[1–4] Both non-specific and lymphocytic interstitial pneumonitis present with clinical and radiological abnormalities that may mimic opportunistic pulmonary infection, especially *Pneumocystis carinii* pneumonia. Patients frequently receive empirical anti-infective therapy before the correct diagnosis is made by lung biopsy.[4]

Before the start of the HIV pandemic, lymphocytic interstitial pneumonitis had been described in case reports in association with a wide range of abnormalities. With the advent of AIDS, it soon became clear that lymphocytic interstitial pneumonitis was being described with increasing frequency, particularly in black African and Afro-Caribbean HIV infected patients. This article reviews current knowledge on the aetiology, pathology, presentation, diagnosis, and treatment of lymphocytic interstitial pneumonitis in HIV infected adults.

METHODS

A Medline search from 1996 to August 2002 was performed using the key works "HIV," "pneumonitis," and "lymphocytes." A further search was performed with the MeSH heading "interstitial lung disorders."A total of 328 articles were found with the combination of "HIV" and "pneumonitis," and the search was limited to the English language, resulting in 262 articles. This search was further focused on articles dealing with lymphocytic interstitial pneumonitis and non-specific interstitial pneumonitis, and 152 articles were identified. A further search was made through Pubmed using the key word "lymphocytic interstitial pneumonitis," which resulted in 64 articles and the search was extended to include related articles, which identified another 34 articles. A search with the key word "lymphocytic interstitial pneumonitis" was also made using Medline, resulting in 106 articles. Ultimately, 228 articles were reviewed.

HISTORY AND EPIDEMIOLOGY

Lymphocytic interstitial pneumonitis was first described in 1996,[5] and may be associated with a variety of autoimmune and lymphoproliferative disorders including Sjøgren's syndrome,[6 7] myasthenia gravis,[8] systemic lupus erythematosus,[9] pernicious anaemia,[10] rheumatoid arthritis, Hashimoto's thyroiditis, lymphoma,[7] autoerythrocyte sensitisation syndrome,[11] chronic active hepatitis, biliary cirrhosis,[12] and multicentric Castleman's disease.[13] It may also be associated with ataxia-telangiectasia,[14] pulmonary alveolar proteinosis, complicated by *Mycobacterium avium-intracellulare* infection,[15] and various immune deficiency states including agammaglobulinaemia,[10] hypogammaglobulinaemia,[12] and common variable immunodeficiency.[16]

An association with retroviral infection was first described in 1986 in relation to HIV-1.[17–19] While common in the HIV infected paediatric population,[20] it appears to be uncommon in adults, occurring in <5% of necropsy case series.[21] Of note, HIV infected children with haemophilia are less commonly affected than children who acquire HIV infection by vertical transmission. This may reflect that few children infected with HIV by blood products were black African or Afro-Caribbean.[22] An association with HIV-2, although rare, has also been reported.[23] Lymphocytic interstitial pneumonitis has also been described in association with HTLV-1 infection in the absence of HIV infection.[24] In HIV infected adults, lymphocytic interstitial pneumonitis has been described in patients from all risk groups although it is most common in black Africans and Afro-Caribbean patients. It appears particularly common in those from Haiti but this may be because the condition has been specifically looked for in this group of patients.[25 26] In contrast, it is rare in white homosexuals.[2 19 25]

AETIOLOGY AND PATHOGENESIS

HIV associated lymphocytic interstitial pneumonitis may represent part of a spectrum of lymphocytic infiltrative disorders.[1 4 25 27–29] Most HIV infected adult patients develop a low grade lymphocytic alveolitis which is usually asymptomatic.[30 31] Some progress to symptomatic alveolitis, either non-specific interstitial pneumonitis or lymphocytic

interstitial pneumonitis. It appears that lymphocytic alveolitis, non-specific interstitial pneumonitis, and lymphocytic interstitial pneumonitis represent a spectrum of lymphoid pneumonitis. Why pulmonary lymphocytic infiltrates in some HIV infected patients manifest as non-specific interstitial pneumonitis rather than lymphocytic interstitial pneumonitis or vice versa remains unclear. It may be that different clades of HIV determine whether a patient develops non-specific interstitial pneumonitis or lymphocytic interstitial pneumonitis.[29]

An association with major histocompatibility complex antigens has been demonstrated. Those with HLA-DR5 and HLA-DR6 in black and HLA-DR7 in white patients are predisposed to develop a systemic lymphocytosis of CD8 T cells with clinically significant diffuse visceral infiltration, known as diffuse infiltrative lymphocytosis syndrome (DILS).[32 33] Involved organs include lung, kidney, liver, stomach, meninges, cranial nerves, motor neurons, parotid and other salivary and lacrimal glands, nasopharynx, bone marrow, spleen, colon, duodenum, thymus, and uvea.[1 32–36]

Possible mechanisms responsible for accumulation of lymphocytes in the pulmonary interstitium include recruitment of circulatory lymphocytes in response to chemoattractants, decreased efflux of cells away from the lung,[27] and an in situ lymphoproliferative response to chronically presented viral antigens or to locally elaborated cytokines, including interleukin 2 and TNFα.[27 37]

The term bronchus associated lymphoid tissue (BALT) describes pulmonary mucosal lymphoid tissue.[38–40] The development and expansion of BALT is a response to local stimulation from inflammation and inhalation of antigens.[25] In the normal lung BALT is seldom seen, being found in fetal and infant lung, and only when evidence of antigenic stimulation was present.[41] In a necropsy study in HIV non-infected patients, expression of BALT was more common in smokers than in non-smokers (82% *v* 14%). Both T and B lymphocytes have been found within the cell population of BALT.[42] It is possible that viral factors, acting with HIV-1, may be one of several factors responsible for the appearance and development of BALT and may also be involved in the immunopathogenesis of lymphoproliferative disorders of the lung seen in HIV infected patients.[25]

Several studies have demonstrated the presence of Epstein-Barr virus (EBV) DNA in lung biopsy specimens from HIV infected children with lymphocytic interstitial pneumonitis.[43–45] Correlation between lymphocytic interstitial pneumonitis and serological evidence of active infection with EBV has also been demonstrated.[28 46] Studies in vitro have shown that EBV may immortalise and transform B cells into lymphoblastoid cells by upregulation of the cellular proto-oncogene, B cell leukaemia-2 (bcl-2) via the latent membrane protein (LMP-1).[47] The presence of EBV LMP-1 protein in airway epithelial cells and overexpression of the cellular bcl-2 protein in lymphoid cells of lung tissue has been demonstrated in patients with lymphocytic interstitial pneumonitis.[48] By contrast, EBV activity has not been detected in lung biopsy specimens from adult HIV patients with lymphocytic interstitial pneumonitis in other studies.[24 35]

Other evidence suggests that HIV infection itself may be involved in the development of lymphocytic interstitial pneumonitis.[27 37] Induction of a lymphocytic interstitial pneumonitis-like syndrome by HIV-1 has been shown in a transgenic mouse model.[49] In vitro EBV infected B cells are particularly susceptible to infection by HIV and may facilitate HIV replication in the lung.[50] By in situ hybridisation, large amounts of HIV RNA have been detected within the germinal centres of lymphoid tissue in an adult HIV infected patient with lymphocytic interstitial pneumonitis.[50] In another patient, p24 antigen was detected in macrophages and the interstitium of a lung biopsy specimen.[3] Other reports describe detection of both HIV antigen and antibody in bronchoalveolar lavage (BAL) fluid of patients with lymphocytic interstitial pneumonitis.[40] In one study, the ratio of HIV specific IgG/total IgG in BAL fluid was higher than in peripheral blood in patients with lymphocytic interstitial pneumonitis. The ratio was lower in patients with other diagnoses.[40 51] Aberrant expression of immunoglobulin heavy chain genes in EBV negative, HIV related lymphocytic interstitial pneumonitis has been demonstrated.[51] These observations suggest that lymphocytic interstitial pneumonitis may be associated with a local humoral response within tissue evoked by HIV infection.[40 51 52] A spectrum of pulmonary lymphoproliferative syndromes, including lymphocytic interstitial pneumonitis has been described in patients infected with human T lymphotropic virus-1.[1 50 53 54]

CLINICAL FEATURES

The most common symptoms of lymphocytic interstitial pneumonitis include non-productive cough and progressive exertional dyspnoea of several weeks' duration.[1 3 12 25] Fever, weight loss, and fatigue are frequently reported.[1 12 25] Pleuritic chest pain and haemoptysis are uncommon and suggest either an alternative diagnosis or that co-pathology is present. Some patients with lymphocytic interstitial pneumonitis may be asymptomatic or have minimal symptoms and the diagnosis is only suggested by the finding of an abnormal chest radiograph (see below). Clubbing is common in children with lymphocytic interstitial pneumonitis and is thought to be secondary to lymphocytic interstitial pneumonitis induced bronchiectasis.[55] Recently, clubbing has been described in an adult in the absence of bronchiectasis.[3] Generalised lymphadenopathy, hepatosplenomegaly, and parotid enlargement are more common in children. In the chest, bi-basal end inspiratory crackles are a consistent finding on lung auscultation. Wheeze and diminished breath sounds may also be present. In many instances, the physical findings are minimal or the physical examination is normal.[1 3 12 25] Some patients with lymphocytic interstitial pneumonitis may present with respiratory symptoms and features of Sjøgren's syndrome[32 33] as part of DILS.

DIAGNOSIS

Clinical and laboratory abnormalities, although highly suggestive, are not specific for lymphocytic interstitial pneumonitis.[1 3 12 25] Measurement of serum LDH enzyme levels is not helpful,[1] as elevations are also observed in other conditions, including *Pneumocystis carinii* pneumonia, pulmonary embolism, bacterial pneumonia, non-specific interstitial pneumonitis, and lymphoma.[1] Dysproteinaemia, usually a polyclonal hypergammaglobulinaemia on serum electrophoresis is common[1 25 26]; IgG is the most frequently elevated immunoglobulin.[12] These abnormalities are also described in asymptomatic HIV infection and so they do not aid diagnosis.

On the plain chest radiograph, an interstitial pattern is commonly seen. This characteristically shows bilateral reticular and ground glass opacities predominantly in the lung bases. These appearances may be difficult to distinguish from infectious causes of a diffuse pneumonitis, including *Pneumocystis carinii* pneumonia and bacterial pneumonia (fig 1), and from non-specific interstitial pneumonitis. The chest radiographic abnormalities occurring in lymphocytic pneumonitis have been divided into three radiographic patterns. In type 1, fine reticular or reticulonodular opacities thought to be due to lymphocytic infiltration of the interstitium are seen. In type 2, further accumulation of lymphocytes is thought to produce larger reticulonodular infiltrate nodules having diameters of between 3 and 5 mm. These appearances may mimic miliary tuberculosis (fig 2). The type 3 pattern is a combination of types 1 and 2, with superimposed areas of alveolar opacities. These alveolar opacities are believed to result from bronchiolar compression caused by more severe lymphocytic infiltration.[56] Lymphocytic infiltration of the submucosa of the respiratory

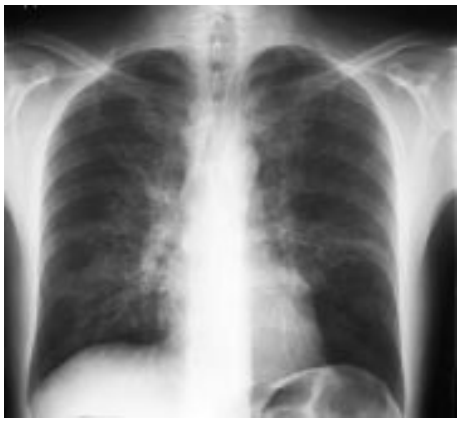

Figure 1 Chest radiograph showing extensive bilateral interstitial infiltrates with ground glass shadowing. Black African HIV positive male, CD4 count 200 cells $\times 10^6$/l, presented with 2 months of increasing dyspnoea, non-productive cough, and fever. Thought initially to have *Pneumocystis carinii* pneumonia but bronchoscopy negative and patient failed to respond to high dose co-trimoxazole. Open lung biopsy revealed lymphocytic interstitial pneumonitis.

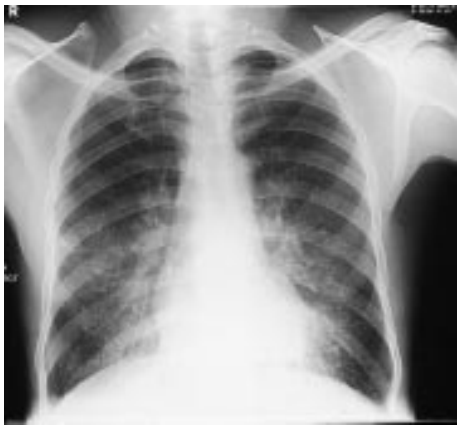

Figure 2 Chest radiograph showing widespread miliary shadowing. Black African HIV positive male, CD4 count 480 cells $\times 10^6$/l (12%) presented with 4 weeks of increasing exertional dyspnoea and non-productive cough. Bronchoscopy was negative and open lung biopsy showed lymphocytic interstitial pneumonitis.

bronchioles may lead to obstruction, inflammation, atelectasis, fibrosis, and finally to bronchiectasis.[57] Pleural effusions are uncommon in adults.[1 25 58] Hilar and mediastinal lymph node enlargement is more common than previously recognised.[56 57]

High resolution computer tomography reveals the extent of the disease and may also demonstrate bronchiectasis and the degree of fibrosis.[55 57–59] Typical appearances include interstitial infiltrates, ground glass shadowing, and centrilobular nodules[3] (figs 3 and 4). These appearances have a wide differential diagnosis including extrinsic allergic alveolitis due to bird fancier's lungs, sarcoidosis, Kaposi's sarcoma, tuberculosis, fungal infections, and *Pneumocystis carinii* pneumonia.[3] Computer tomography may also help discriminate between fibrotic and reversible inflammatory disease.[60 61]

Imaging of the lung using the radionuclide gallium-67 has been performed in patients with lymphocytic interstitial pneumonitis.[2 26 33] Several patterns of intrapulmonary uptake have been described, these include focal and diffuse uptake and no uptake within the lung. These appearances have been described not only in lymphocytic interstitial pneumonitis but also in patients with *Pneumocystis carinii* pneumonia, bacterial pneumonia, and mycobacterial infections. Thus, patterns of gallium-67 uptake in the lung do not aid in diagnosis.[51] High

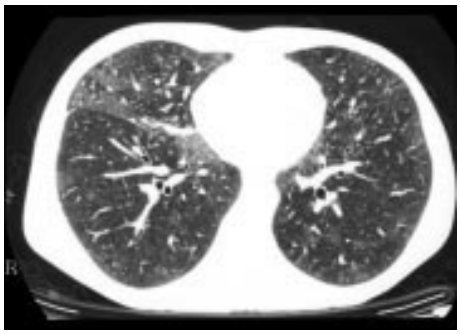

Figure 3 High resolution computed tomograph through the lung bases showing patchy ground glass shadowing. White HIV positive male, CD4 count 500 cells $\times 10^6$/l, presented with 6 months increasing exertional dyspnoea. Bronchoscopy was negative for *Pneumocystis carinii* and other pathogens. Open lung biopsy revealed lymphocytic interstitial pneumonitis.

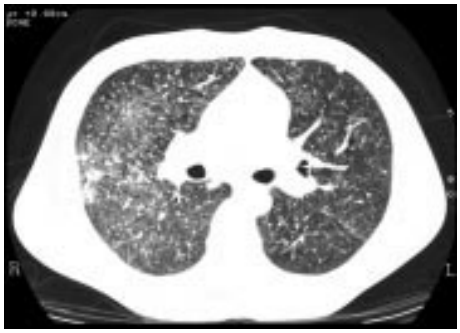

Figure 4 High resolution computed tomograph through the lungs, just below the level of the carina, showing extensive miliary shadowing mimicking *M tuberculosis*. Same patient as figure 2.

resolution computer tomography is more helpful than gallium-67 scanning in guiding the method of biopsy and directing the bronchoscopist to the diseased lung segment in order to maximise diagnostic yield.[62 63]

Pulmonary function tests usually demonstrate a restrictive pattern with a reduced or normal total lung diffusion capacity.[1 3 12 40] Obstructive airway disease has occasionally been reported.[64] Arterial blood gas measurements are unhelpful as they may reveal a normal Pao_2, or mild to profound hypoxaemia with an increased alveolar to arterial oxygen gradient,[12] findings that also occur in *P carinii* pneumonia[65] and other infectious causes of a diffuse pneumonitis. The diagnosis of lymphocytic interstitial pneumonitis is made by transbronchial or open lung biopsy.[1 3 4 29] The diagnostic yield from transbronchial biopsy is lower than that from open lung biopsy and the procedure may result in a pneumothorax. Open lung biopsy may be needed in the case of non-specific findings from transbronchial biopsy and is the preferred method of obtaining lung tissue in many centres.[3 29 65]

Macroscopically, the lungs and the pleura appear normal.[29] Microscopically, diffuse linear interstitial thickening with occasional distinct nodules or follicles, some of them adjacent to the airways and pulmonary arteries, are seen[29 56]; rarely areas of confluence occur. Histological features range from diffuse interstitial infiltrates of lymphocytes, plasma cells, and histiocytes,[29 56 66 67] to more patchy, dense cellular infiltrates with lymphoid follicles and germinal centres. The lymphocytes are usually polyclonal and demonstrate different stages of activation.[29 56 66 67] Giant cells and histiocytes may also be seen.[67] In areas of follicular predominance, immunoblasts and histiocytes containing cytoplasmic cellular debris may be found.[29] Non-caseating granulomata have been reported in between 20–50% of cases.[3 12 29 56 66 67] Of note, no vasculitis or

necrosis is found and other findings include hyperplasia of type 2 pneumocytes.[4 29 67] The infiltrate usually involves the alveolar septae, subpleural areas, intralobular septae and lymphatics running along the bronchovascular bundles. In some cases, the lymphocytic infiltration may be extensive, extending to and consolidating the alveoli.[29 56 66 67] Lymphocytic infiltration in the bronchiolar walls has been demonstrated in only a few cases.[3 29] The lymphoid aggregates may impinge on the walls of the terminal and respiratory bronchioles, producing variable degrees of bronchiolar stenosis and a clinical picture consistent with bronchiolitis.[29 56] With chronicity, lymphocytes may be replaced with fibrosis, and airspace consolidation may be replaced with honeycombing and centrilobular nodules with cysts.[29 56 66–68] The histology of lymphocytic interstitial pneumonitis differs from non-specific interstitial pneumonitis mainly in the extent and volume of cellular infiltration and the association with secondary type 2 pneumocyte hyperplasia. Histologically, the distinction between these two conditions may not always be clear cut.[4 29]

The differential diagnosis histologically includes other disorders that are characterised by interstitial lymphoid proliferation. *P carinii* pneumonia may induce a predominantly lymphoplasmacytic infiltrate and may be erroneously diagnosed as lymphocytic interstitial pneumonitis.[67 68] Fungal and mycobacterial infections should be excluded when histiocytic proliferation and granulomata formation become prominent.[68] In the latter stages of lymphocytic interstitial pneumonitis, the prominent interstitial fibrosis may be difficult to distinguish from cryptogenic fibrosing alveolitis, and other common types of interstitial pneumonitis.[67–69]

NATURAL HISTORY

HIV associated lymphocytic interstitial pneumonitis usually occurs when the CD4+ T lymphocyte count is still within the normal range.[3 4 32 33] By contrast, non-specific interstitial pneumonitis usually occurs at a later stage, patients typically have CD4+ T lymphocyte counts around 200 cells $\times 10^6$/l.[4 25] However, both conditions have been reported in patients whose CD4+ T lymphocyte counts are within the normal range.[1 4 25]

The natural history of lymphocytic interstitial pneumonitis is variable.[1 25] The duration of symptoms at the time of diagnosis of HIV associated lymphocytic interstitial pneumonitis is between 1 month and 11 years.[1] Symptoms are usually progressive, but may remain stable for months without treatment and sometimes improve spontaneously.[70] Mortality data are inexact, in part this is due to lack of reported follow up and in part to the anecdotal nature of some reports. By contrast, most cases of non-specific pneumonitis resolve spontaneously, usually do not develop respiratory insufficiency, and do not themselves lead to death.[1 4 25]

TREATMENT

As the clinical course of lymphocytic interstitial pneumonitis is unpredictable, assessment of specific therapeutic interventions is difficult. In the general population, before AIDS, response of lymphocytic interstitial pneumonitis to immunosuppression with glucocorticoids was poor or irregular.[1 7 9 71] A combination of glucocorticoids and additional immunosuppression with azathioprine was successful in a singe case.[72]

In HIV infected patients assessment of the prognosis and outcome of lymphocytic interstitial pneumonitis is made more difficult because the illness is significantly affected by the natural history and response to treatment of the underlying HIV infection. Several reports from before antiretroviral therapy became available describe no deterioration in lymphocytic interstitial pneumonitis without specific intervention.[25] In contrast with the general population, other reports of HIV infected patients with lymphocytic interstitial pneumonitis describe improvements in most cases in response to glucocorticoids.[32–33 73–75] In these reports, the dose and duration of glucocorticoid therapy is variable with therapy being given from several weeks only to chronic suppressive therapy.[32 33 73–75] Some reports describe an initial response with relapse on withdrawal or dose reduction of glucocorticoids. More aggressive immunosuppression using chlorambucil has been reported as successful in a single case.[32 33]

The response of HIV associated lymphocytic interstitial pneumonitis to intervention with antiretroviral therapy is variable. Zidovudine, as monotherapy, has been used in three patients.[76 77] In two patients a response was observed,[74] in a third patient with more advanced HIV infection no response occurred.[77 78] One report described significant improvement with chloroquine in a child with lymphocytic interstitial pneumonitis:[78] Of note, the patient was also receiving zidovudine. Recently, improvement in clinical symptoms, radiology and pulmonary function tests have been described in an HIV infected adult patient with lymphocytic interstitial pneumonitis treated with combination antiretroviral therapy (consisting of three nucleoside analogues). The improvement in lymphocytic interstitial pneumonitis was paralleled by reduction of HIV viral load to below the limits of detection and by improvement in CD4+ T lymphocyte counts.[3] There are no reports of treatment of lymphocytic interstitial pneumonitis with protease inhibitor or non-nucleoside reverse transcriptase inhibitor containing regimens of antiretroviral therapy, but hypothetically, as these combinations are more effective in lowering the HIV viral load and increasing the CD4+ T lymphocyte count,[79] they might be expected to bring about improvement in the clinical course of lymphocytic interstitial pneumonitis.

CONCLUSION

Lymphocytic interstitial pneumonitis was rarely encountered by clinicians before the onset of the HIV pandemic. The clinical presentation, findings on examination, chest radiographic and laboratory abnormalities may be difficult to distinguish from infectious causes of diffuse pneumonitis which occur more commonly in the HIV infected adult. Lung biopsy is required in order to make a diagnosis. Treatment of the underlying HIV infection with combination antiretroviral therapy may have a beneficial effect on the symptoms and prognosis of lymphocytic interstitial pneumonitis.

CONTRIBUTORS

SD and RFM jointly proposed the project; SD carried out the literature search and wrote the first draft of the manuscript; RFM critically commented on subsequent drafts and co-wrote the final version of the manuscript with SD.

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