ISSN: 0975-833X

Available online at http://www.journalcra.com

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

International Journal of Current Research
Vol. 13, Issue, 05, pp.17177-17181, May, 2021

DOI: https://doi.org/10.24941/ijcr.41362.05.2021

REVIEW ARTICLE **OPEN ACCESS**

SARS-COV-2 (COVID19), MUCORMYCOSIS AND DIABETIC PATIENTS: A LITERATURE REVIEW

[1*]Dr. Ankit Jha and [2]Dr Pooja Yadav

[1]Junior Resident at Aruna Asaf Ali government hospital
[2]MDS (Endodontics) Dr. BhimraoAmbedkar University, India

ARTICLE INFO

Article History:
Received 14th February, 2021
Received in revised form
05th March, 2021
Accepted 19th April, 2021
Published online 15th May, 2021

Key Words:
Covid19, Mucormycosis, Diabetes, Immunocompromised patients.

ABSTRACT

Mucormycosis (MCM) is a life-threatening infection that carries high mortality rates despite recent advances in its diagnosis and treatment. Mucormycosis occurs in patients who are immunocompromised because of diabetic ketoacidosis, neutropenia, organ transplantation, and/or increased serum levels of available iron. Because of the increasing prevalence of diabetes mellitus, cancer, and organ transplantation, the number of patients at risk for this deadly infection is increasing. This literature review emphasis on the types, risk factor, diagnosis and treatment of mucormycosis.

Citation: Dr. Ankit Jha (MBBS), Dr Pooja Yadav (MDS, Endodontist). "SARS-CoV-2 (COVID19), Mucormycosis and Diabetic patients: A Literature Review", *2021. International Journal of Current Research, 13, (05), 17177-17181.*

INTRODUCTION

The 2019 novel coronavirus (2019-nCoV) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first reported in Wuhan, Hubei province in China, quickly spread to other parts of the world forming a global pandemic[1].The disease pattern of COVID-19 can range from mild to life-threatening pneumonia with associated bacterial and fungal coinfections[2]. Due to the associated comorbidities (e.g., diabetes mellitus, chronic obstructive pulmonary disease) and immunocompromised conditions (e.g., corticosteroid therapy, ventilation, intensive care unit stay), these patients are prone to develop severe opportunistic infections. There are reports of the development of severe opportunistic infections such as oropharyngeal candidiasis, pneumocystis jiroveci pneumonia, pulmonary aspergillosis, bloodstream candida infections, etc., in patients affected with COVID-19 disease[3]. There are also few isolated case reports of rhino-orbital mucormycosis in COVID-19 disease. Some authors described that a significant decrease in lymphocyte count and an increase of neutrophil count together with an inflammatory storm, occur more frequently in patients who developed severe COVID-19 and co-infections.[4]

In India compared with the western world, including a high incidence of this disease; uncontrolled diabetes and diabetic ketoacidosis as the principal risk factor; rhino-orbito-cerebral (ROC) form as the most common clinical presentation; isolated renal mucormycosis as a new entity; and a wide and varied spectrum of pathogens involved in such infections[5]. Seasonal variations in incidence of mucormycosis with respect to temperature, rainfall and humidity have also been noted[6]. This literature review emphasis on the types, risk factor, diagnosis and treatment of mucormycosis.

What is Mucor mycosis?: Mucormycosis (sometimes called zygomycosis) is a serious but rare fungal infection caused by a group of molds called mucormycetes. These fungi live throughout the environment, particularly in soil and in decaying organic matter, such as leaves, compost piles, or rotten wood[7].People get mucormycosis by coming in contact with the fungal spores in the environment. .

Types of Mucor mycosis

- **Rhinocerebral (sinus and brain) mucormycosis (ROC)** is an infection in the sinuses that can spread to the brain. This form of mucormycosis is most common in people with uncontrolled diabetes and in people who have had a kidney transplant.[8,9]

- **Pulmonary (lung) mucormycosis** is the most common type of mucormycosis in people with cancer and in people who have had an organ transplant or a stem cell transplant.
- **Gastrointestinal mucormycosis** is more common among young children than adults, especially premature and low birth weight infants less than 1 month of age, who have had antibiotics, surgery, or medications that lower the body's ability to fight germs and sickness.[10]
- **Cutaneous (skin) mucormycosis**: occurs after the fungi enter the body through a break in the skin (for example, after surgery, a burn, or other type of skin trauma). This is the most common form of mucormycosis among people who do not have weakened immune systems.
- **Disseminated mucormycosis** occurs when the infection spreads through the bloodstream to affect another part of the body. The infection most commonly affects the brain, but also can affect other organs such as the spleen, heart, and skin.

Types of fungi that most commonly cause mucormycosis

Examples are: *Rhizopus* species, *Mucor* species, *Rhizomucor* species, *Syncephalastrum* species, *Cunninghamella bertholletiae*, *Apophysomyces* species, and *Lichtheimia* (formerly *Absidia*) species.[9]

Based on the clinical presentations, ROC is the most common form of mucormycosis in India, possibly due to its association with uncontrolled diabetes and diabetic ketoacidosis.[5,11] According to the multiple case series reported from our tertiary care centre in North India, the prevalence of different clinical types amongst mucormycosis cases is: ROC (48– 55%), cutaneous (13–15%), pulmonary (7–17%), disseminated (5–12%), gastrointestinal (5–13%) and isolated renal (5–14%).[12,13]

Rhinocerebral (sinus and brain) mucormycosis (ROC): The initial symptoms of rhinocerebral mucormycosis are consistent with either sinusitis or periorbital cellulitis[14,15] and include eye or facial pain and facial numbness, followed by the onset of conjunctival suffusion, blurry vision, and soft tissue swelling[16,17]. Fever is variable and may be absent in up to half of cases[15]; white blood cell counts are typically elevated, as long as the patient has functioning bone marrow[17]. If untreated, infection usually spreads from the ethmoid sinus to the orbit, resulting in loss of extraocular muscle function and proptosis. Marked chemosis may also be seen. The infection may rapidly extend into the neighboring tissues. Onset of signs and symptoms in the contralateral eye, with resulting bilateral proptosis, chemosis, vision loss, and ophthalmoplegia, is an ominous sign that suggests the development of cavernous sinus thrombosis. Upon visual inspection, infected tissue may appear normal during the earliest stages of spread of the fungus. Infected tissue then progresses through an erythematous phase, with or without edema, before onset of a violaceous appearance, and finally the development of a black, necrotic eschar as the blood vessels become thrombosed and tissue infarction occurs[18]. Infection can sometimes extend from the sinuses into the mouth and produce painful, necrotic ulcerations of the hard palate[18.]

Pulmonary (lung) mucormycosis: may develop as a result of inhalation or by hematogenous or lymphatic spread. Symptoms of pulmonary mucormycosis include dyspnea, cough, and chest pain.[19] Angioinvasion results in necrosis of tissue parenchyma, which may ultimately lead to cavitation and/or hemoptysis, which may be fatal if a major blood vessel is involved.

Cutaneous mucormycosis may be primary or secondary. Primary infection is usually caused by direct inoculation of the fungus into disrupted skin and is most often seen in patients with burns or other forms of local skin trauma, and can occur in patients who are not immunosuppressed. Primary infection produces an acute inflammatory response with pus, abscess formation, tissue swelling, and necrosis. The lesions may appear red and indurated and often progress to black eschars. Secondary cutaneous infection is generally seen when the pathogen spreads hematogenously; lesions typically begin as an erythematous, indurated, and painful cellulitis and then progress to an ulcer covered with a black eschar.

Gastrointestinal mucormycosis is less common than the other clinical forms and is believed to result from ingestion of the organism. It typically occurs in malnourished patients or premature infants. The stomach, colon, and ileum are most commonly affected. Non-specific abdominal pain and distension, nausea, and vomiting are the most common symptoms, and gastrointestinal bleeding can occur. It is the most common form of mucormycosis among neonates and is challenging to diagnose partly because of its clinical resemblance to necrotizing enterocolitis, a far more common disease.[20]

Disseminated mucormycosis may follow any of the forms of mucormycosis described above but is usually seen in neutropenic patients with a pulmonary infection. The most common site of spread is the brain, but the spleen, heart, skin, and other organs can also be affected.

Diabetes as a risk factor: Amongst the diabetic patients, poorly controlled type II diabetes is the most common risk factor for mucormycosis, being involved in nearly 44–88% of the cases mainly from north to south India, with nearly half of them exhibiting ketoacidosis.[6,12,13] Type I diabetes (10–15%) and secondary diabetes have also been detected in some patients.[13,21,22] In contrast, diabetes was the risk factor in only 36% of the global series of 929 cases,[23] 17% of the Trans-European series,[24] 16% of France series, 6% of Belgium serie and 18% of Italy series[25]. It should be noted, however, that as confounding factors, renal failure and alcoholism related chronic liver disease have also been detected in patients along with diabetes in India.[12] Several factors relate the unique predisposition of diabetic patients to mucormycosis. Firstly, diabetes and ketoacidosis render the phagocytic cells dysfunctional. Both neutrophils and macrophages exhibit an impaired chemotaxis and defective killing by both oxidative and non-oxidative pathways under such conditions, although the precise mechanisms mediating these remain to be elucidated.[26,27] Secondly, patients with diabetic ketoacidosis have an acidic serum pH with elevated levels of free iron, which is a major nutrient element governing susceptibility to Mucorales.[26,28] Thirdly, elevated levels of glucose and iron, similar to those observed during diabetic ketoacidosis, increase the expression of GRP-78. GRP78 is a glucose-regulated protein belonging to the HSP-70 family, which is mainly present in the endoplasmic reticulum where it mediates several cellular processes as a chaperon, including protein folding, degradation of misfolded proteins, regulation of calcium

homeostatis and sensing the endoplasmic reticulum stress.[26,27,28] Recent studies indicate that a fraction of GRP-78 is also translocated to the cell surface in many cell types,41 wherein it acts as the receptor mediating penetration and damage of endothelial cells by Mucorales, leading to the observed angioinvasion.[26]Mice with diabetic ketoacidosis have an increased expression of GRP-78 in sinus, lungs and brain, and anti-GRP-78 serum can protect such mice from mucormycosis, indicating a plausible role of GRP-78 overexpression in susceptibility of diabetics to this disease.[26,28] The presence of diabetes mellitus and the individual degree of hyperglycaemia also seems to be independently associated with COVID-19 severity and increased mortality[29,30]. Furthermore, the presence of typical complications of diabetes mellitus (CVD, heart failure and chronic kidney disease) increases COVID-19 mortality

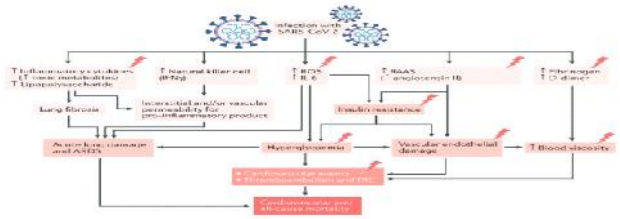

Figure 1: Lightning bolts indicate mechanisms that are accentuated in patients with type 2 diabetes mellitus (T2DM). Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[31]can lead to increased levels of inflammatory mediators in the blood, including lipopolysaccharide[32], inflammatory cytokines[33] and toxic metabolites. Modulation of natural killer cell activity (increased or decreased) and IFNγ production can increase the interstitial and/or vascular permeability for pro-inflammatory products[33]. In addition, infection with SARS-CoV-2 leads to increased reactive oxygen species (ROS) production[33]. These effects lead to lung fibrosis, acute lung damage and acute respiratory distress syndrome (ARDS). ROS production and viral activation of the renin–angiotensin–aldosterone system (RAAS) (via increased angiotensin II expression) cause insulin resistance, hyperglycaemia and vascular endothelial damage[33], all of which contribute to cardiovascular events, thromboembolism and disseminated intravascular coagulation (DIC). Infection also causes increases in the clotting components fibrinogen and D-dimer[34], leading to increases in blood viscosity[33]and vascular endothelial damage, and associated cardiovascular events, thromboembolism and DIC.

How is mucormycosis diagnosed?: Healthcare providers consider your medical history, symptoms, physical examinations, and laboratory tests when diagnosing mucormycosis. Healthcare providers who suspect that you have mucormycosis in your lungs or sinuses might collect a sample of fluid from your respiratory system to send to a laboratory. Rapid diagnostic methods include biopsy, KOH mount and Calcofluor stain. Mucor is difficult to routinely culture. Biopsy remains the mainstay of diagnosis and the benefits of the procedure outweigh the risk, even in a 'difficult to access' location or in the presence of coagulopathy. In a tissue biopsy, in which a small sample of affected tissue is analyzed in a laboratory for evidence of mucormycosis under a microscope or in a fungal culture. You may also need imaging tests such as a CT scan of your lungs, sinuses, or other parts of your body, depending on the location of the suspected infection.

Several antifungals now available for mucormycosis treatment

Four factors are critical for eradicating mucormycosis: rapidity of diagnosis, reversal of the underlying predisposing factors (if possible), appropriate surgical debridement of infected tissue, and appropriate antifungal therapy.

Mucormycoses: an indication of emergency surgery

Current guidelines recommend antifungal treatment, surgical debridement, and correction of risk factors. Surgical debridement has to be extensive, involving all necrotic areas for rhino-oculo-cerebral infection, and repeated surgical procedures are recommended to achieve local control and improve outcome[35]. For pulmonary mucormycosis, the indication and timing of surgical management outside emergency care (hemoptysis) is still unclear[36]. In a European series of 230 patients, surgical treatment reduced mortality by 79% [37], leading to discuss surgery when feasible for any localization, however mandatory for rhino-cerebro-oculo-cerebral and post-traumatic Mucor mycosis.[38]

Antifungal treatment

Table 1. Antifungal strategies for mucormycosis

Therapy	Antifungal	Pros	Cons
Established therapies			
	Amphotericin B deoxycholate (AmB)	50 years experience	Toxicity
		Cidal	Resistance seen in individual isolates
	Liposomal amphotericin B (LAmB)	Less toxic than AmB	Most expensive polyene
		Improved CNS penetration	
		High-dose LAmB (15 mg/kg/day) superior to AmB (1 mg/kg/day) in murine model	
		Superior to AmB in retrospective clinical study	
	Amphotericin B lipid complex (ABLC)	Less toxic than AmB	Inferior CNS penetration vs. LAmB in one rabbit study
			Not superior to placebo or AmB in murine model even at high doses (up to 30 mg/kg/day)
			No comparative clinical data published
Investigational/adjunctive therapies			
	Itraconazole	Superior toxicity profile Successful case reports	Poor activity in animal models despite in vitro susceptibility
			Breakthrough mucormycosis described during prophylactic itraconazole
	Posaconazole	More effective than itraconazole in animal models	Not yet FDA approved
		Possible combination with polyene therapy, but no data available	Activity inferior to AmB in murine models

	Caspofungin	Very low toxicity	Virtually no clinical data for mucormycosis
		Synergistic with ABLC in murine model	Minimal activity as monotherapy in murine model
		FDA approved (not for mucormycosis)	
	Iron chelation	Theoretical benefit in combination with antifungals	No effective agents are FDA approved
	Hyperbaric oxygen	Nontoxic	Not widely available
	Cytokine therapy	In vitro activity	Limited data
		Successful case reports	Expensive Toxicity profile unclear

CONCLUSION

COVID-19 is associated with a significant incidence of secondary infections, both bacterial and fungal probably due to immune dysregulation. Additionally, the widespread use of steroids/monoclonal antibodies/broad-spectrum antibiotics as part of the armamentarium against COVID-19 may lead to the development/exacerbation of preexisting fungal diseases. Physicians should be aware of the possibility of invasive secondary fungal infections in patients with COVID-19 infection especially in patients with preexisting risk factors and should enable early diagnosis and treatment with the subsequent reduction of mortality and morbidity. The use of therapeutic agents should be monitored to achieve a therapeutic effect at the lowest dose and shortest durations. The use of broad-spectrum antibiotics, especially in the absence of infection, should be re-evaluated.

REFERENCES

Farnoosh G, Alishiri G, Hosseini Zijoud SR, Dorostkar R, Jalali Farahani A. Understanding the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease (COVID-19) based on available evidence-A narrative review J Mil Med. 2020;22:1–11

Mehta S, Pandey A. Rhino-orbital mucormycosis associated with COVID-19 Cureus. 2020;12:e10726

Salehi M, Ahmadikia K, Badali H, Khodavaisy S. Opportunistic fungal infections in the epidemic area of COVID-19: A clinical and diagnostic perspective from Iran Mycopathologia. 2020;185:607–11

Liu J, Li S, Liu J, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine. 2020;55:102763.

Chakrabarti A, Singh R. The emerging epidemiology of mould infections in developing countries. Curr Opin Infect Dis 2011; 24: 521–6

Nithyanandam S, Jacob MS, Battu RR, Thomas RK, Correa MA, D'Souza O. Rhino-orbito-cerebral mucormycosis. A retrospective analysis of clinical features and treatment outcomes. Indian J Ophthalmol 2003; 51: 231–6.

Richardson M. The ecology of the Zygomycetes and its impact on environmental exposureexternal icon. Clin Microbiol Infect. 2009 Oct;15 Suppl 5:2-9.

Song Y, Qiao J, Giovanni G, Liu G, Yang H, Wu J, Chen J. Mucormycosis in renal transplant recipients: review of 174 reported casesexternal icon. BMC Infect Dis. 2017 Apr; 17(1): 283.

Abdalla A, Adelmann D, Fahal A, Verbrugh H, Van Belkum A, De Hoog S. Environmental occurrence of *HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC120253/" Madurella mycetomatis* HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC120253/", the major agent of human eumycetoma in Sudanexternal icon. J Clin Microbiol. 2002 Mar; 40(3): 1031–1036.

Vallabhaneni S, Mody RK. Gastrointestinal mucormycosis in neonates: a reviewexternal icon. Current Fungal Infect Rep. 2015.

Chakrabarti A, M. D. epidemiology of mucormycosis in India. Curr Fungal Infect Rep 2013; 7: 287–92.

Chakrabarti A, Chatterjee SS, Das A et al. Invasive zygomycosis in India: experience in a tertiary care hospital. Postgrad Med J 2009; 85: 573–81.

Chakrabarti A, Das A, Mandal J et al. The rising trend of invasive zygomycosis in patients with uncontrolled diabetes mellitus. Med Mycol 2006; 44: 335–42.

Dhiwakar, M., A. Thakar, and S. Bahadur. 2003. Improving outcomes in rhinocerebral mucormycosis-early diagnostic pointers and prognostic factors. *J. Laryngol Otol.*117:861-865

Talmi, Y. P., A. Goldschmied-Reouven, M. Bakon, I. Barshack, M. Wolf, Z. Horowitz, M. Berkowicz, N. Keller, and J. Kronenberg. 2002. Rhino-orbital and rhino-orbito-cerebral mucormycosis. *Otolaryngol. Head Neck Surg.*127:22-31

Khor, B. S., M. H. Lee, H. S. Leu, and J. W. Liu. 2003. Rhinocerebral mucormycosis in Taiwan. *J. Microbiol. Immunol. Infect.*36:266-269

Thajeb, P., T. Thajeb, and D. Dai. 2004. Fatal strokes in patients with rhino-orbito-cerebral mucormycosis and associated vasculopathy. *Scand. J. Infect. Dis.*36:643-648

Petrikkos, G., A. Skiada, H. Sambatakou, A. Toskas, G. Vaiopoulos, M. Giannopoulou, and N. Katsilambros. 2003. Mucormycosis: ten-year experience at a tertiary-care center in Greece. *Eur. J. Clin. Microbiol. Infect. Dis.*22:753-756.

Tedder, M., J. A. Spratt, M. P. Anstadt, S. S. Hegde, S. D. Tedder, and J. E. Lowe. 1994. Pulmonary mucormycosis: results of medical and surgical therapy. *Ann. Thorac. Surg.*57:1044-1050.

Vallabhaneni S, Mody RK. Gastrointestinal mucormycosis in neonates: a reviewexternal icon. Current Fungal Infect Rep. 2015 Sept

Singh V, Singh M, Joshi C, Sangwan J. Rhinocerebral mucormycosis in a patient with type 1 diabetes presenting as toothache: a case report from Himalayan region of India. BMJ Case Rep 2013; 2013: pii: bcr2013200811.

Ganesh R, Manikumar S, Vasanthi T. Rhinocerebral mucormycosis in an adolescent with type 1 diabetes mellitus: case report. Ann Trop Paediatr 2008; 28: 297–300

Roden MM, Zaoutis TE, Buchanan WL et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis 2005; 41: 634–53.

Skiada A, Pagano L, Groll A et al. Zygomycosis in Europe: analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group on Zygomycosis between 2005 and 2007. Clin Microbiol Infect 2011; 17: 1859–67

Pagano L, Valentini CG, Posteraro B et al. Zygomycosis in Italy: a survey of FIMUA-ECMM (Federazione Italiana di

Micopatologia Umana ed Animale and European Confederation of Medical Mycology). J Chemother 2009; 21: 322–9.

Ibrahim AS, Spellberg B, Walsh TJ, Kontoyiannis DP. Pathogenesis of mucormycosis. Clin Infect Dis 2012; 54(Suppl. 1): S16–22.

Chinn RY, Diamond RD. Generation of chemotactic factors by Rhizopus oryzae in the presence and absence of serum: relationship to hyphal damage mediated by human neutrophils and effects of hyperglycemia and ketoacidosis. Infect Immun 1982; 38: 1123–9.

Artis WM, Fountain JA, Delcher HK, Jones HE. A mechanism of susceptibility to mucormycosis in diabetic ketoacidosis: transferrin and iron availability. Diabetes 1982; 31: 1109–14

Lee AS. GRP78 induction in cancer: therapeutic and prognostic implications. Cancer Res 2007; 67: 3496–9

Liu M, Spellberg B, Phan QT et al. The endothelial cell receptor GRP78 is required for mucormycosis pathogenesis in diabetic mice. J Clin Invest 2010; 120: 1914–24

Holman, N. et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. *Lancet Diabetes Endocrinol.* 8, 823–833 (2020). This article shows that increased COVID-19-related mortality is associated with glycaemic control and cardiovascular and renal complications of diabetes mellitus.

Barron, E. et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. *Lancet Diabetes Endocrinol.* 8, 813–822 (2020).

Nansen, A., Christensen, J. P., Marker, O. & Thomsen, A. R. Sensitization to lipopolysaccharide in mice with asymptomatic viral infection: role of T cell-dependent production of interferon-gamma. *J. Infect. Dis.* 176, 151–157 (1997)

Teuwen, L. A., Geldhof, V., Pasut, A. & Carmeliet, P. COVID-19: the vasculature unleashed. *Nat. Rev. Immunol.* 20, 389–391 (2020)

Cummings, M. J. et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York city: a prospective cohort study. *Lancet* 395, 1763–1770 (2020).

Vironneau P, Kania R, Morizot G, Elie C, Garcia-Hermoso D, Herman P, Lortholary O, Lanternier F; French Mycosis Study Group. Local control of rhino-orbito-cerebral mucormycosis dramatically impacts survival. Clin Microbiol Infect. 2014 May;20(5):O336-9. doi: 10.1111/1469-0691.12408. Epub 2013 Nov 6. PMID: 24118291.

Chretien ML, Legouge C, Pagès PB, Lafon I, Ferrant E, Plocque A, Favennec C, Estivalet L, Bottolier-Lemallaz E, Dalle F, Bastie JN, Bernard A, Caillot D. Emergency and elective pulmonary surgical resection in haematological patients with invasive fungal infections: a report of 50 cases in a single centre. Clin Microbiol Infect. 2016 Sep;22(9):782-787. doi: 10.1016/j.cmi.2015.12.029. Epub 2016 Jan 22. PMID: 26806254.

****

Hamming, I. et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J. Pathol.* 203, 631–637 (2004)