

Smoking, COPD, Infection and Lung Cancer: How Are They Interconnected?

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Abstract:

A case of an elderly ex-smoker chronic obstructive pulmonary disease (COPD) patient with controlled type 2 diabetes mellitus (T2DM) as comorbid was followed-up for 10 years. His stable COPD in the course of time slowly declined to multiple acute exacerbation (AE)-COPD and multiple hospital admissions. High-dose systemic corticosteroids given during AE-COPD with prolonged oral steroids continuation led to depressed immunity that ended with severe immunosuppression, causing sepsis and chronic heart failure (CHF) with non-ST elevated myocardial infarction (NSTEMI) and worsening of COPD in his ninth year follow-up. This immunosuppression also triggered the emergence of lung cancer by allowing malignant cell to evade immune surveillance. Fortunately patient is survived and recovered to stable COPD.

Introduction.

Smoking is a major epidemic worldwide that is known to cause cardiovascular disease, COPD and lung cancer.¹ According to World Health Organization (WHO), there are 61.4 million current smoker in Indonesia (23.25% of total population), predominantly male (67%), and they start smoking at the average age of 17.6 years old. About 88% of these smokers use *kretek* cigarette or clove flavored cigarette.³ COPD is currently the fourth leading cause of death in the world and mainly affects smokers and former smokers. The risk of developing COPD increases with the amount of cigarette exposure.⁴ It is known that the prevalence of lung cancer is significantly higher in patients with COPD than in the average nonsmoking population, reflecting the impact of cigarette smoking in both diseases.⁵ COPD has been reported to be an independent risk factor for lung cancer regardless of cigarette smoking, and about 1% of COPD patients develop lung cancer every year, which may be associated with genetic susceptibility to cigarette smoke. COPD patients have a higher prevalence of certain comorbidities, including coronary artery disease, congestive heart disease, other cardiovascular diseases, regional malignancies (mainly lung cancer) and neurological diseases.⁶

Case presentation

Mr. OT, 72 years old male, came from north Sumatra. He was first seen on September 7, 2008 for a consultation complaining short of breath while walking for 5 meters distance that he had been suffered for 2 months. He was formerly a heavy smoker of 5 packs cigarette

per day for almost 40 years, then quit for 15 years and never admitted to the hospital. He had seen many doctors in his hometown also in Medan and Penang. His oxygen saturation was 96% on room air, BP 180/85, pulse 102 bpm, fine crackles were heard on the right and left lower lobe. His chest X-ray and chest CT scan were within normal limit with EKG showing old inferior infarction but his echocardiogram showed left ventricular hypertrophy and ejection fraction 68%. His lung function test showed FVC 1.85 (73%); FEV₁ 0.95 (49%); PFR 240 l/m. His CBC and blood chemistry were normal with fasting glucose 122 mg/dl, post prandial glucose 239 mg/dl, and HbA1c.^{5,8}

He was diagnosed with COPD category GOLD 3B and hypertensive heart disease, coronary artery disease, and controlled type 2 diabetes mellitus. After 2 months on Symbicort and Spiriva treatment his performance improved and he was able to walk for 1 km.

On November 2009 he was admitted to Harapan Kita National Heart Center in Jakarta for coronary catheterization and no coronary stenosis was found. On May 2011 he had a stroke and was admitted to Penang Adventist Hospital and had pulmonary edema as its complication but his cardiac status was unremarkable. In 2013, diabetic nephropathy was detected as his creatinine and uric acid rose up above normal limit. He also got influenza vaccination annually.

On September 2014, patient was diagnosed with congestive heart failure (CHF) with pulmonary arterial hypertension (PAH) and dilated heart chamber on echocardiogram, along with oral candidiasis, anemia, low sodium and potassium level due to prolonged diuretic treatment, but his chest X-ray was unremarkable. In 2015, his carcinoembryonic antigen (CEA) was elevated to 7.5. His chest X ray was still unremarkable but his lung function decreased to FVC 1.00 (40%); FEV₁ 0.76 (37%); and PFR 230 l/m.

In early 2017, patient had AE-COPD that led to hospitalization for the first time and several more acute exacerbations afterward that did not require hospitalization, but required prolonged systemic corticosteroid use in addition to his regular long-acting beta-agonist and corticosteroids (LABACS) and long-acting muscarinic-receptor antagonist (LAMA) inhaler. Due to high level of IgE (557) and considering that he might also had asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS), an anti IgE was given monthly and resulted in decreased IgE (385) after six months. During that period of time, he also showed slight renal function impairment with estimated glomerular filtration rate (eGFR) of 47. His chest X-ray showed slightly enlarged heart with concentric left ventricular hypertrophy (LVH), normal ejection fraction on his echocardiogram, and his lung function was getting better as shown by FVC 1.71 (68%); FEV₁ 1.26 (71%); PFR 220 l/m, also his noncontrast HRCT scan was consistent with centrilobular emphysema.

In early 2018 he was again admitted to a hospital in Penang for AE-COPD and readmitted to St. Borromeus Hospital in Bandung on March 15, 2018 due to shortness of breath after exertion. He was transferred to the ER and diagnosed with sepsis causing CHF, NSTEMI and AE-COPD leading to ICU admission, where he was intubated and ventilated mechanically. Subsequently he got multiorgan dysfunction while extended spectrum beta-lactamase (ESBL)-producing *Klebsiella pneumoniae* was recovered from his urine, as well as multidrug-resistant (MDR) *Pseudomonas aeruginosa* and ESBL-producing *Klebsiella pneumoniae* were recovered from his bronchial aspirate along with low CD4 count (53). On the 7th day in the ICU, a bloody tracheal aspirate was noted and did not subside after several days of hemostatic drugs so bronchoscopy was done on March 29, 2018 and it was noted that the source of the bleeding was from the mucosal lining of the right upper lobe bronchus where a biopsy was taken. Subsequently the pathologist reported a finding of adenosquamous carcinoma from the specimen. A second bronchoscopy was done to ablate the *in situ* lung cancer with Argon Plasma Cauterization, also a second biopsy was done and this time it was adenocarcinoma. Interesting finding on the patient is about his immune system, the low CD4 count that was initially and rose to 116 then decreased to 60 when he was discharged from the hospital, but later increased to 427. No human immunodeficiency virus (HIV) or tuberculosis (TB) infection were detected but past viral infections noted were herpes simplex (HS)-1 and 2, cytomegalovirus (CMV), rubella, and toxoplasma.

Final diagnoses on May 6, 2018 when he was discharged for home ventilation was respiratory failure, hypoventilatory failure, anemia, AE-COPD, DM, chronic kidney disease (CKD), uremia, sepsis, immunocompromised infection, *Klebsiella pneumoniae* UTI, CAD, CHF, AF, and adenocarcinoma *in situ* at the bifurcation of RUL, TONOMO stage 0, EGFR mutation not detected, PDL-1 was positive on more than 50% of tumor cells, patient Performance Status (PS) was 4.

On the following month while he was still on long-term home ventilation with continuous positive airway pressure (CPAP), a third bronchoscopy and a third biopsy was done but no cancer cells found and his CD4 increased to 427. On the second month of home ventilation that was in August 6, 2018, he was able to be weaned from the ventilator. After another month of active mobilizing physiotherapy, patient was able to walk again and he flew back to his hometown in north Sumatra. On June 2019 he was still doing well and taking his regular LABACS and LAMA inhaler.

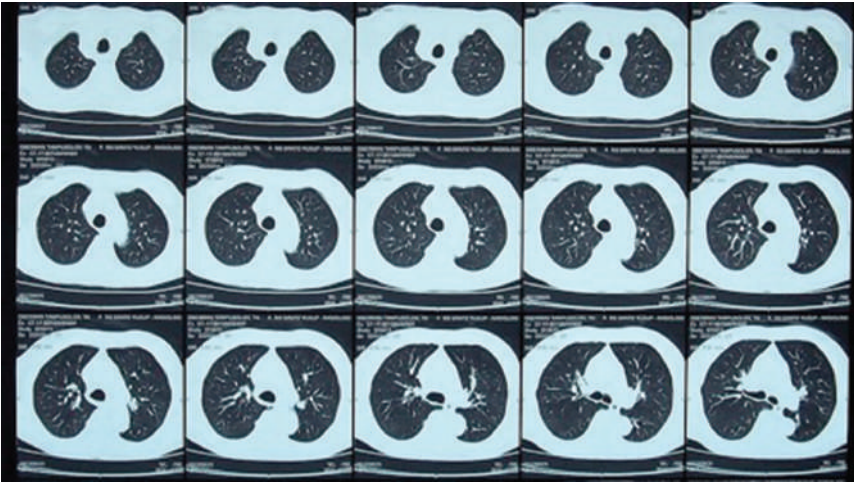


Figure 1. Chest CT Scan of August 30, 2017 was unremarkable.



Figure 2. Chest X ray on March 15, 2018 showed enlarged heart with clear lung

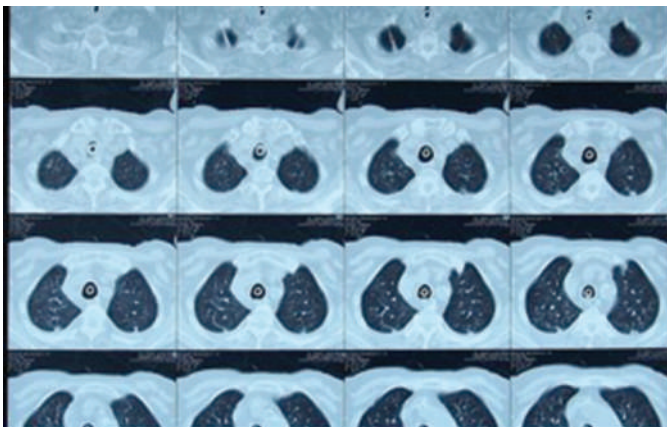


Figure 3. Chest CT scan on April 2, 2018, while patient was intubated and on mechanical ventilation was also unremarkable.

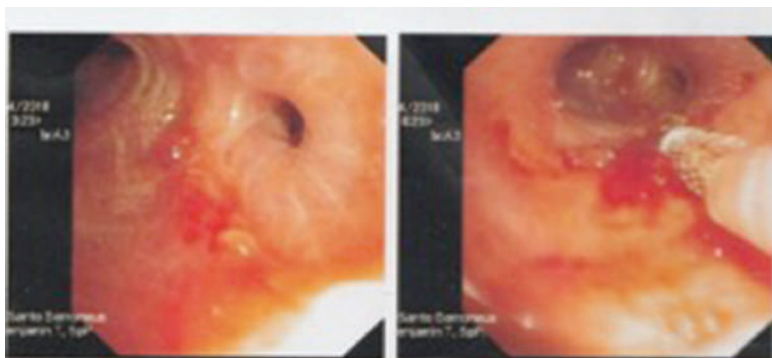


Figure 4. On the 7th day in the ICU a bloody tracheal aspirate was noted so bronchoscopy was done and found that the source of the bleeding was from the mucosal lining of the right upper lobe bronchus where a biopsy was taken.

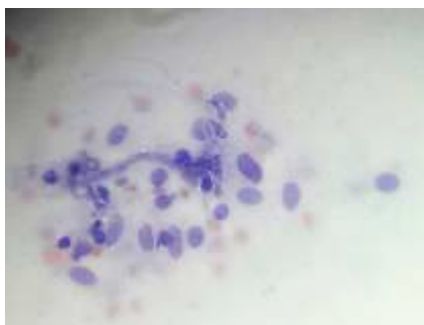


Figure 5. Cancer cells nuclei stained blue and had variable sizes but bigger than red blood cells in this cytological specimen.

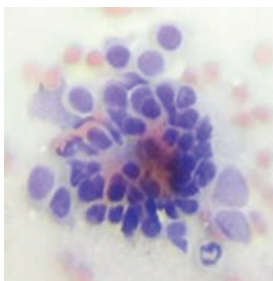


Figure 6. Cluster of cancer cells nuclei stained blue and had variable sizes forming glandular formation with 2 bigger nuclei on the right lower picture as part of squamous cell carcinoma. This type was adenosquamous carcinoma with mostly adenocarcinoma component.

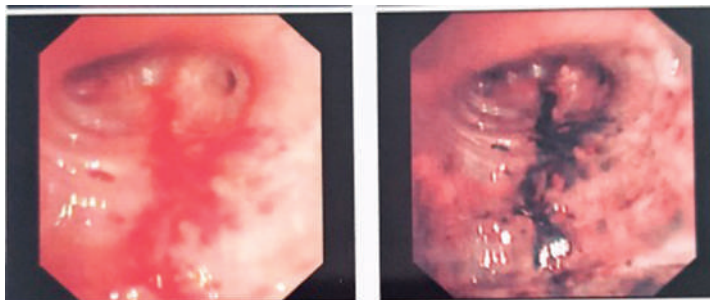


Figure 7. Carcinoma *in situ* on the right upper lobe bronchus as seen with ordinary light (left) and with Narrow Band Imaging light (right) where the submucosal capillary blood vessels was seen dark blue.

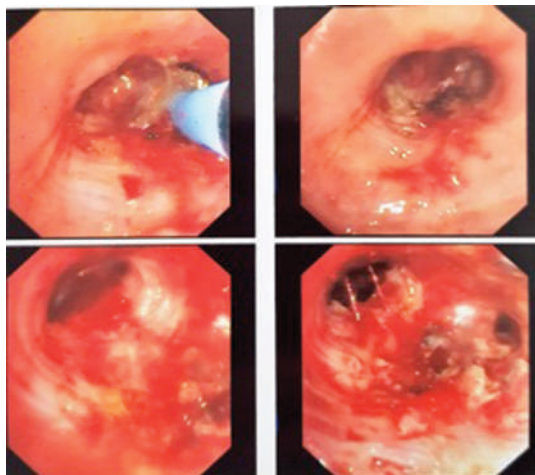


Figure 8. Applying Argon Plasma Coagulation to the lesion at 30 watt energy output and 0.8 liter / minute flow rate with ERBE machine on June 07, 2018.



Figure 9. Chest X ray on August 14, 2018 after 2 weeks of extubation was unremarkable.

Discussion

Cigarette Smoke (CS) is a complex mixture of thousands of chemicals generated upon the burning or heating of tobacco leaves and it contains thousands of chemicals that have cytotoxic, mutagenic, carcinogenic, or antigenic properties.⁷ *Kretek* cigarettes contain tar and nicotine, 25 mg and 1.6 mg, respectively, that are significantly higher than nonclove cigarettes.⁸

This patient smoked 200 pack per year of *kretek* cigarettes before quitting for 15 years. Gaseous and particulate CS constituents first interface with the immune system at the mucosal surfaces lining of the oral cavity, sinuses, and airways. Several toxins present in CS have immunomodulatory effects. CS also contains trace amounts of microbial cell components, including bacterial lipopolysaccharides. These and other CS constituents induce chronic inflammation at mucosal surfaces and modify host responses to exogenous antigens.

The effects of CS on immunity are far-reaching and complex; both proinflammatory and suppressive effects may be induced. The net effect of CS on immunity depends on various variables, including dose and type of tobacco, route and duration of exposure, and the presence of other factors at the time of immune cell stimulation, such as Toll receptor ligands or other inflammatory mediators. CS impairs innate defenses against pathogens, modulates antigen presentation, and promotes autoimmunity.⁷ Current smoking was associated with 10 inflammation markers after correcting for multiple testing, encompassing several components of the immune/inflammation response. Levels of seven of these markers (interleukin [IL]-15, IL-1RA, IL-1 β , IL-16, stem cell factor, soluble interleukin 6 receptor, and soluble vascular endothelial growth factor receptor 3) were lower among current smokers.¹

The pathogenic mechanisms of COPD are not clear but are most likely diverse. Increased numbers of activated polymorphonuclear leukocytes and macrophages release elastases in a manner that cannot be counteracted effectively by antiproteases, resulting in lung destruction. The primary offender has been found to be human leukocyte elastase, with synergistic roles suggested for proteinase-3 and macrophage-derived matrix metalloproteinases (MMPs), cysteine proteinases, and a plasminogen activator. Additionally, increased oxidative stress caused by free radicals in CS, the oxidants released by phagocytes, and polymorphonuclear leukocytes, all may lead to apoptosis or necrosis of exposed cells.⁹

Inhaled corticosteroid (ICS) is used in COPD⁴ and it increases the risk of mycobacterial and other infections, and it should be born in mind when monitoring people on these drugs, but on the other side, ICS also have protective roles, it reduces the risks and the harm of some infections.¹⁰ Observational studies from the “real-world” in the use of systemic corticosteroid have consistently shown dose-dependent increases in the risk of serious infections as well as certain opportunistic infections (e.g. herpes zoster, tuberculosis, and pneumocystis jiroveci pneumonia/PJP).¹¹ Glucocorticoids cause immunosuppression, decreasing the function and/or numbers of neutrophils, lymphocytes (B cells and T cells), monocytes, macrophages, and the anatomical barrier function of the skin. This suppression, if large enough, can cause immunodeficiency manifestations, including T cell deficiency, humoral immune deficiency and neutropenia. The major mechanism for this immune suppression is through inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B). NF- κ B is a critical transcription factor involved in the synthesis of many mediators (i.e., cytokines) and proteins (i.e., adhesion proteins) that promote the immune response. Inhibition of this transcription factor, therefore, blunts the capacity of the immune system to mount a response. Glucocorticoids suppress cell-mediated immunity by inhibiting genes that code for the cytokines IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8 and IFN- γ , the most important of which is IL-2. Smaller cytokine production reduces the T cell proliferation. However, glucocorticoids not only reduce T cell proliferation, but also lead to another well-known effect, glucocorticoid-induced apoptosis. The effect is more prominent in immature T cells inside in the thymus, but peripheral T cells are also affected. The exact mechanism regulating this glucocorticoid sensitivity lies in the Bcl-2 gene. Glucocorticoids also suppress the humoral immunity, by causing B cells to express smaller amounts of IL-2 and of IL-2 receptors. This diminishes both B cell clone expansion and antibody synthesis. The diminished amounts of IL-2 also cause fewer T lymphocyte cells to be activated.¹² This mechanism explained why this patient got sepsis with low CD4 count after using prolonged high-dose ICS and frequent courses of high-dose systemic corticosteroids for his AE-COPD. After recovering from sepsis and tapering off his corticosteroids dose, his CD4 count increases to 116 and then to 427 at one month after being discharged from hospital.

Cancer originates from a single transformed cell (cancer stem cell), that due to genetic instability, commonly become genetically heterogeneous exhibiting multiple phenotypes in term of morphology and physiology. This cell grows, but has a prolonged period during which the developing tumor is so small it is undetectable by all means, as seen in this patient for instance. His chest CT scan done one year prior in August 30, 2017 was unremarkable and also his chest X-ray on March 15, 2018 only showed enlarged heart with clear lung. Repeated chest CT scan on April 2, 2018 while he was intubated and on mechanical ventilation did not detect any lung nodule, while on March 29, 2018 bronchoscopy was already done due to persistent hemoptysis and adenosquamous carcinoma was seen at the right upper lobe bronchus, so it was assume to be *in situ* carcinoma. At some point, according to the natural history of lung cancer, the tumor is sufficiently large to be detectable if an imaging study is done (i.e., CT or positron emission tomography), but it is still too small to cause any clinical symptoms. Eventually, a change in the patient's well-beingness prompts medical attention and a diagnosis is made, as in this case a sepsis event and a persistent hemoptysis, but the difference in this case is the lung cancer was still undetected by CT scan. This sepsis event with low CD4 count described his suppressed systemic immunity that cannot hold down the cancer in the dormant state anymore. The time from the initial malignant transformation to clinical detection is the preclinical phase, and generally is at least 3/4 of the entire life of the tumor. If a diagnosis is made by an intercurrent imaging study before the onset of symptoms, the time between this incidental diagnosis and the usual diagnosis at clinical presentation represents the lead time. The time between the diagnosis and the patient's death is the survival time. Obviously, if diagnosis is made earlier, the survival time will be longer (even without any active treatment) because of the lead time. On the other hand, malignant tumors lead to death not only because of growth of the primary tumor mass, but because of the capacity of tumor to metastasize to distant sites. There is a wide variation in tumor growth rates. Lung cancer is a heterogeneous disease with a spectrum of growth characteristics. The presence of circulating tumor cells was unrelated to tumor stage. An acquired genetic change in the tumor cells (i.e. an angiogenesis factor) may be what determines how and when circulating cells develop the ability to form actively growing metastases. Changes in the host immune system or microenvironment (i.e., chemokines) may be the key.¹³

Hemoptysis in this patient and bronchoscopic finding of intense submucosal hyper-vascularization on Narrow Band Imaging (NBI) and easily bleed uneven mucosa may show vascular endothelial growth factor (VEGF) and VEGF receptors (VEGFR) to be elevated, supporting the notion that angiogenesis develops early in lung carcinogenesis.¹⁴ The tumor microenvironment (TME) is dynamic and complex,

comprising cancer cells, cancer-associated stromal cells and their extracellular products. Cancer-associated fibroblasts (CAFs), which are the primary stromal cells within the TME, may contribute to tumor neoangiogenesis via proteomic and degradomic alterations.¹⁵

The meaning of intralesional heterogeneity is that tumor cells acquire mutations, some of which provide survival advantages to selective clones of cells in which subclones expand independently, acquiring different mutations over time and this multiple subclonal populations can coexist together. Intratumoral heterogeneity (ITH) has now been described in various malignancies, including lung cancer.¹⁴ Separated biopsy specimen done on 2 occasional bronchoscopy showed adenocarcinoma with small element of squamous cell carcinoma, that confirmed the present of ITH morphologically but ITH also presented at molecular level. On the molecular level, it is possible to distinguish at least two large categories of ITH, one of which is mostly clonal, transmitted to the daughter cells, and the other one is functional nonclonal.

There is a lower extent of information on epigenetic evolution, which is also mostly clonal. Gene promoter methylation, general hypomethylation of tumor DNA, histone methylation and deacetylation are very common in cancer and are as relevant as genetic alterations interaction between clonal genomic instability of cancer and the microenvironment, that lead to a nonclonal phenotypical functional plasticity which is related to autocrine and paracrine interactions with a quite wide phenotype range. Beside the phenotypical functional plasticity, ITH is also related to a stochastic type of plasticity that can affect any single cell. Even in cell lines, each cell is different from the others with respect to efficiency and efficacy of the single cell machinery with various time and level of gene expression.¹⁶

After this patient recovered from his sepsis and his CD4 had increased, an Argon Plasma Ablation (APC) was done on June 07, 2018 at this second bronchoscopy which was 3 months apart. The lesion was stable and no hemoptysis seen which mean that his immune system has recovered, indicated by increasing CD4 count to 427 and a new equilibrium was reached. APC reduces the tumor burden significantly and reached a next new level of equilibrium in which his cancer lies dormant one year after APC and hopefully for years to come. Residual cancer cells cannot be determined and lobectomy is not an option in this case because of his COPD.

In summary this case supports the theory of immune-editing in term of lung cancer which includes immune surveillance, tumor equilibrium, tumor escape mechanism and intratumor heterogeneity. The interaction of smoking with chronic inflammation causes COPD, effect of immune suppression cause by multiple AE-COPD on the emergence of lung cancer was also discussed. Fortunately, the patient survived and recovered to stable COPD with no signs of cancer recurrence.

Conclusions

A case of COPD patient due to past cigarette smoking on a long term follow-up approximately 10 years was presented. His symptoms slowly getting worse with acute exacerbations needing multiple courses of antibiotic and high-dose systemic corticosteroids which led to systemic immunity suppression that ended up with sepsis. At his lowest immunity state, his lung cancer emerged by giving symptom of hemoptysis. It is assumed that long-term inflammation in the field of injury and cancerization created COPD and also generated lung cancer stem cell. Immuno-editing by mean of immune-surveillance will eliminate these newly generated cancer cells or otherwise achieved equilibrium for a certain period of time. When disequilibrium occurred, such as suppressed immunity due to multiple courses of high-dose systemic corticosteroids, the cancer emerged clinically. Within one week, the first symptom of hemoptysis appeared, indicating an active neoangiogenesis occurrence. With immune recovery, a new equilibrium was reached and APC ablation reduced the tumor burden significantly to reach a new level of equilibrium, in which his cancer lies dormant one year after APC.

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2
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Pilih Jawaban A, B, atau C, pada pertanyaan di bawah untuk jawaban yang benar dengan mencantumkan pilihan pada kotak jawaban (untuk Medicinus versi cetak)

NO	PERTANYAAN
1	<p>Pernyataan berikut yang benar terkait chronic obstructive pulmonary disease (COPD) adalah</p> <ul style="list-style-type: none">A. Risikonya meningkat dengan adanya paparan asap rokokB. Merupakan penyebab kematian keempat tertinggi di duniaC. Merupakan salah penyakit pernafasan kronisD. Semua jawaban benar
2	<p>Dampak buruk dari paparan asap rokok disebabkan karena beberapa sifat senyawa yang terkandung di dalamnya, kecuali</p> <ul style="list-style-type: none">A. MutagenikB. KarsinogenikC. SedatifD. Antigenik
3	<p>Variabel berikut memengaruhi efek total dari paparan asap rokok pada imunitas tubuh yaitu</p> <ul style="list-style-type: none">A. Jenis rokok yang digunakanB. Durasi merokokC. Keberadaan mediator inflamasiD. Semua jawaban benar
4	<p>Pernyataan yang benar terkait pendekatan patofisiologi terjadinya COPD adalah</p> <ul style="list-style-type: none">A. Destruksi jaringan paru dan pengaruh stress oksidatifB. Tidak dipengaruhi paparan radikal bebasC. A dan B benarD. A dan B salah
5	<p>Berikut adalah pernyataan yang benar mengenai penggunaan <i>corticosteroid</i> pada pasien COPD, kecuali</p> <ul style="list-style-type: none">A. <i>Corticosteroid</i> sering diresepkan pada penderita COPD untuk membantu mengendalikan gejalaB. <i>Corticosteroid</i> merupakan satu-satunya golongan obat yang direkomendasikan pada kasus COPDC. Penggunaan <i>corticosteroid</i> dalam jangka panjang dapat berpengaruh pada terjadinya supresi sistem imunD. Pengguna <i>corticosteroid</i> jangka panjang perlu diawasi terhadap kemungkinan timbulnya manifestasi immunodefisiensi
6	<p>Pada pasien dalam kasus ini, kondisi sepsis yang disertai dengan status penurunan fungsi sistem imun dapat dilihat dari</p> <ul style="list-style-type: none">A. Tingkat kesadaranB. Tingginya produksi lendir saluran pernafasanC. Kadar CD4 yang rendahD. Tidak ada jawaban yang benar





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NO	PERTANYAAN
7	Dalam kasus kanker, yang dimaksud dengan <i>survival time</i> adalah A. Waktu sejak diagnosis ditegakkan sampai pasien sembuh B. Waktu sejak dimulainya terapi sampai pasien sembuh C. Waktu sejak saat gejala mulai dirasakan sampai diagnosis ditegakkan D. Waktu sejak saat diagnosis ditegakkan sampai pasien meninggal
8	<i>Hemoptysis</i> yang dialami oleh pasien berkaitan dengan perkembangan dini kanker paru yang melibatkan proses vaskularisasi yang dikenal dengan istilah A. Angiogenesis B. Glukoneogenesis C. Tumorigenesis D. Tidak ada jawaban yang benar
9	Pernyataan yang benar tentang perjalanan penyakit pasien pada kasus ini adalah A. Riwayat merokok menyebabkan inflamasi kronis yang memicu terjadinya PPOK B. Riwayat eksaserbasi berulang, penggunaan corticosteroid jangka panjang, menyebabkan penurunan imunitas yang memungkinkan sel kanker mudah berkembang C. A dan B benar D. A dan B salah
10	Pada kasus ini, tindakan yang dipilih sebagai modalitas untuk menangani <i>adenosquamous carcinoma in situ</i> pada pasien adalah A. Argon Plasma Ablation (APC) B. Antigen-Presenting Cell (APC) C. Gamma Knife surgery D. Loop electrosurgical excision procedure (LEEP)

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