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CaseReport

PulmonaryNoncaseatingGranulomaAssociatedwithInfliximabinCrohn'sDisease:TheFirstCaseReportedinChina

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2. Keywords

Crohn'sdisease;Pulmonarymanifestation;Granuloma;TNFinhibitor; Infliximab.

1.Abstract

Crohn'sDisease(CD)isa mainkindofInflammatoryBowel Disease(IBD) whoseetiologyis un- clear butcomplexand the effective treatmentisdeficient. Since TumorNecrosisFactor (TNF) inhibitorusedtotreatCD,greatlyimprovementhasbeenseeninpatients'clinicalsymptomandliving condition. However,somecomplications have beenemerged gradually. Here wereport aCDpatient whousedtotreatedbyInFliXimab(IFX)combined withnoncaseatinggranulomatousinflammationinlunglesion. Asfarasweknow,thecurrentstudyisthefirsttodescribepulmonarygranulo- ma associated withIFX inCD fromChina. The rare complicationreminds that the extra intestinal granuloma ofCDmayberelatedtoanti-TNFalphaagentandphysiciansshouldkeepawarenessof its recurrence. It is essential to take the potential of TNF inhibitor induction of granulomas into accountandpreventpatientsundergoingunnecessaryTNFinhibitortreatment.Also,thesafetyand adverse reactions ofTNF inhibitor should be evaluated prudentlyina wider range.

3. Introduction

TumorNecrosis Factor (TNF) is a kind of cytokine that associate withmultiplediseasessuchasinfectiousdisease,immunedisease, tumor. It has been demonstrated that TNF inhibitor can effectively improve the clinical symptom and related laboratory dataof autoimmune diseases through altering the immune response. Paradoxically,aseriesofcasesofTNFinhibitorinducednoncase ating granulomatous inflammation in rheumatological conditions whichinvolvedmultipleorganshavebeenreported[1].Inallthree kinds of TNF inhibitors, etanercept is more related with non case ating granuloma than the others [2]. The current study is, to our acknowledgement, the first to describe infliximab (IFX) induced non case ating granulomas in lung of a patient being treated for Crohn'sdiseaseinChina.Thesafetyand adverseeventofanti-TNF alpha agent should be long-term monitored in thefuture.

4. CaseReport

A60-year-oldwomanwithahistoryof10-yearCDpresented with a history of fever, cough, shortness of breath, diarrheaand loss of appetite for 5 days. She had a pyrexia of 39 Celsius and coughed with white foam sputum accompanied by right chest pain.IleocecalCD had beendiagnosed 10 yearsago and the patienttreated with infliximab (IFX), mesalamine, prednisolone, vitamins and nutritional treatment. She discharged after symptom control and take Azathioprine(AZA) for maintenance therapy. Five years later she underwent colectomy in other hospital and accepted blood transfusionduringoperation. She was a life-longnon-smoker and her families were all in good condition.

On her admission, the physics examination was unremarkable despite a slightly rough breathing sounds in two lungs. Laboratory data showed a white blood account of 6.80×109/L (88.8% neutrophils,0.60%eosinophils,0.10% basophil,7.20% monocytes,3.30%lymphocytes) and microcytic hypochromic anemia was taken into account for MCV 70.2 fl, MCH 22.6 pg, MCHC 322g. Blood test also showed an increase active of inflammation: ESR45mm/h;Creactiveprotein19mg/L;autoimmunerelatedantibodieswereallnegative;AngiotensinConvertingEnzyme(ACE) levelwasinnormalrange.StoolanalysisshowedOccultBloodTest (OBT), fungi and parasites were negative. Phlegm culture, blood culture and T-spot were negative. She was started on antibiotics quadruple therapy includes cefpimoxime, moxifloxacin, imipenem and cefoperazone, ambroxol and sodophylline used for pro-

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ductivecoughand wheezingrespectively. Unfortunately,thelung lesion was not improved obviously and further examination had beencarriedout.WefoundthatshewasalifelongnonsmokerandhadnohistoryofrelevantlungdiseasesChestcomputedtomography revealed bilateral pleura thickness, consolidation in right middle lobe and small nodules in right upper lobe (Figure 1).She received immuno suppressants as long-termtreatment and lead to a weak immune function, which pushed the differential diagnosis withinfectious diseases into a dilemma and the lesionbiopsywas imperative. Electronic bronchoscopybiopsyshowed bronchitis in rightmiddlelobe,mucosalinflammatorycellsinfiltrationandseveralsmallgranulomas(Figure2).BronchoAlveolarLavage(BAL) showed a small number of inflammatory cells and columnar epithelialcells.PulmonaryFunction(PFT)testwasnormalandbronchialdilationtestwasnegative.Inconsiderationofgranulomatous lung disease and organizing pneumonia was suspected, she was treated with methylprednisolone 40mg intravenous injection and then switched to oral methylprednisolone 16mg/12mg bid. Patients showed good compliance during the cortico therapyand no adverseeffectssuchascentralobesity,pepticulcers,andinfections occurred. Her symptoms had responded evidently and imaging manifestationhadalsoimproved.ShewastoldtoreviewchestCT regularly after discharge.

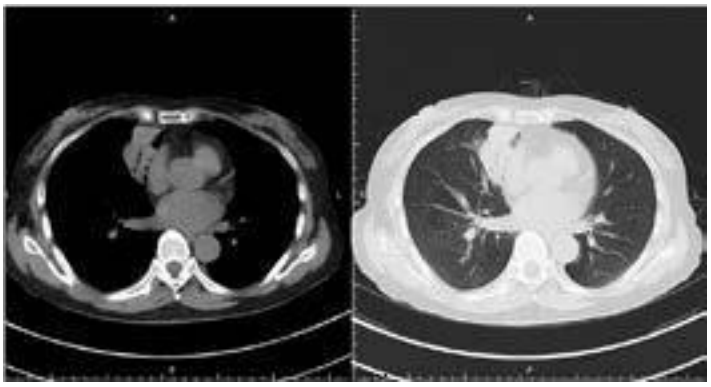

Figure1: Chestcomputedtomographyshowsbilateralpleurathickness,consolidationinrightmiddle lobe and small nodules in right upperlobe.

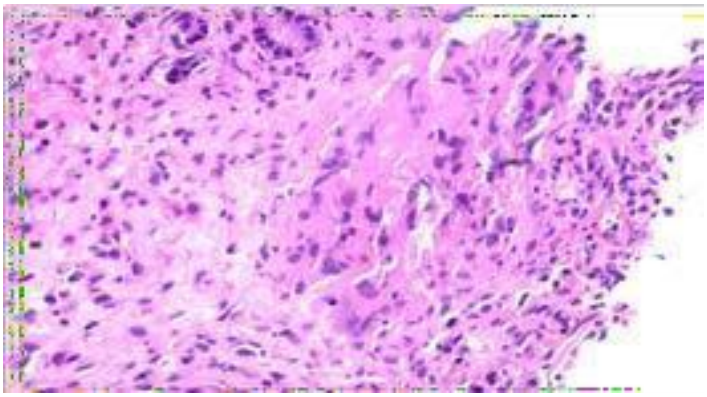

Figure 2: The pathological biopsy in lung lesions. Electronic bronchoscopy biopsy showedbronchitis in right middle lobe, mucosal inflammatory cells infiltration and several smallgranulomas

5. Discussion

TNFα has been recognized as an essential cytokine factor of inducing granuloma and the using of TNFα inhibitor could prevent theformationofgranulomatherapeutically.Recentyears,theform of granuloma has been described as a rare adverse reactionof anti-TNFα treatmentrepeatedly in rheumatic disease. Most cases were found non case ating granuloma in lung, hilar lymph node andskinlesion[1,3,4].Otherorgans,suchasbone marrow[5] and liver[6]havealsobeenobserved.Thesegranulomasinvolvedwith multi-organs were all found between 1 to 69 months onset of the TNFα inhibitor therapy [1,4].Among the commonly used TNFα inhibitors, it is etanercept (ETA) that more probably induces the extraintestinal granulomathan infliximab (IFX) andadalimum-ab (ADA) [1,3,4] and this discrepancy may caused by the different pharmacological mechanism. In conclusion, IFX could block TNFαindifferentpointsonitspathwaywhile ETAleaveasumof TNFα in active form that participate in the forming of granuloma [7-10].Meanwhile,itisseamsthatthereisnocorrelationbetween the resolution of extra intestinal granuloma and the use of TNFα inhibitor,becauseofwhether maintainingorinterruptingtheoriginalTNFαinhibitortreatmentorswitchtoanotherTNFαinhibitor can lead to the resolution of the pulmonary granuloma, and steroids is equally feasible[1,4].

Given that TNFα inhibitor is applied to CD later, fewer corresponding adverse reaction has been reported. Indeed, the mechanism by which TNFαinhibitors causes extra intestinal granuloma is not clear and clinicians generally lack of full understanding of it. To us acknowledge, it is the first case of pulmonary non case atinggranulomaassociatedwith IFXin Chinaandthereisonlyone pleural granuloma associated with IFX in CD has been reported before [2].Our patient showed negative in infectious diseases and theratioof CD4/CD8 in BAL was normal, thusthediagnosisoftuberculosisorsarcoidosiswasexcluded.Besidesadversereactionof IFXwecannotfindanappropriatecausetoexplainthepulmonary noncaseatinggranuloma.Thismaysuggestthatwhen CDpatientswith a history of anti-TNFα agent medication shows extra intestinalgranulomatouslesions,TNFαinhibitorassociatedadversereaction should be considered. In addition, clinicians should be clear about the indications for TNFα inhibitors and the timing of optimal medication, thereby avoiding patients receiving unnecessary TNFα inhibitors treatment.

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