Letter to the Editor

What we have known, what we do not know?—clonality of multifocal pulmonary ground-glass opacities

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Background

In this issue of *JTD*, it published two comments from Dr. Detterbeck and Dr. Lee (1,2) on our recent research article in Thorax, which reported clonally related in two cases of multiple ground-glass opacities (GGOs). In the comments, the authors agreed with most of our perspectives in the original article in Thorax. We thank the authors giving highly comments on our publication. Dr. Detterbeck wrote in his comment, "*the reality is that we are all like blind men, trying to characterize an entity that we are not able to observe in its entirety. We must be careful not to overemphasize a particular perspective and not to go too far in drawing conclusions from particular observations*". We could not agree more with such comment.

Perspectives

Clinically, it is much easier to conclude that two tumors are different than defining clonally related. Laboratory investigations to distinguish between these possibilities have resulted in multiple publications (3-7). But a consensus has not been reached. Many studies assessed particular mutations to define clonality, assuming that a match of a few (one to five) markers defines a single clone whereas a difference defines multiple primaries (3-6). Given some widely recognized recurrent mutations, reliability on mutational pattern should be moderated by the general prevalence of the mutations. The reverse side of the medal, which we also should keep in mind, discordance between primary and metastatic sites in obviously metastatic disease is not uncommon existing.

The key question here is, could tumors with multiple identical genetic mutations be determined as from single origin. Could similar mutations from different sites of one patient be caused by a common etiology? We give highly agreement with most of the conclusions in the International Association for the Study of Lung Cancer (IASLC) consensus in 2016 (8-11). The committee, to some extent, also concluded that, evidence that two lesions are metastatic or separate primary tumors must be viewed as only suggestive because of inconsistencies in the available data. In the consensus, laboratory investigations were also included. They suggested tumors may be considered to be arising from a single tumor source if matching breakpoints are identified by comparative genomic hybridization (CGH). Such being the case, why tumors could not be considered to be metastatic if they match the criteria identified by whole-exome sequencing. In the published research in 2016, Nature communications by Liu *et al.* (12), they demonstrated even in the context of identical genetic background and environmental exposure, the development of multiple primary lung adenocarcinomas from individual patient can be driven by distinct molecular events in different tumors. Lung tumors of the same individuals are no more similar to each other than are lung adenocarcinomas of different patients from TCGA cohort matched for tumor size and smoking status. In the

TCGA cohort 20/8,413 exonic mutations shared between any tumor pairs, as well as 1/884 exonic mutations shared between any tumor pairs in Liu *et al.*'s series. However in our series, lesions L6 and L7 of patient 1 shared 19 non-synonymous mutations with a total of 40 non-synonymous mutations in these two lesions (excluding the EGFR p.L858R variant). The degree of shared mutations was far higher than that of TCGA and Liu's series, particularly since these were noted in rarely reported genes, could not be explained as convergent evolution, and indicated that the two lesions represented intrapulmonary metastasis. At the same we also ruled out the possibility of field cancerization.

Then we come to the question, do these patients experience worse prognosis as for the metastatic disease? Although many studies have demonstrated that GG/L tumors exhibit rather indolent behavior and have excellent clinical outcomes (13-15), as well as GGOs in the two patients in our report, indolent behavior could not be the evidence the two tumors are not metastatic. Never there was a consensus stated manifestation of metastatic dissemination was a surrogate for poor outcome. The other way around, more than one study have shown clonally related airway cancers were not necessarily with ominous clinical impact (16,17). The biologic behavior of cancer is intricate, and impacted by many aspects, such as tumor cell factors, host characteristics, and multiple interactions between them. What we are able to observe may be just a tip of the iceberg. Through joint forces with each other, the IASLC committee considered multiple perspectives and types of evidence, but did not make clearly defining of the nature of the multifocal GG/L lesions. They just concluded that the level of understanding was insufficient yet. So part purpose of our study was just shedding some light on the area of uncertainty about the generation of multifocal GGOs. We wish more attention will be paid on this process to understand more clearly of the natural history of GGOs.

If these GGOs were metastatic lesions, another question comes up now, how these GG/L lesions metastasis from one to another? The process of metastasis is highly complex. In 1889, the English surgeon Stephen Paget first proposed the "seed and soil" hypothesis (18). Nearly 40 years later, Paget's theory was challenged by James Ewing, who again proposed that metastasis occurs by purely mechanical factors determined by the anatomy of the vascular and lymphatic channels that drain the primary tumor (19). These two theoretical systems of metastasis remain widely accepted even in nowadays. Accumulative evidence demonstrated it is overly simplistic to think of the process of metastasis as one governed by physical routes (i.e., lymphogenous, hematogenous). "Aerogenous" dissemination via the airways was suggested >60 years ago, implying dissemination via airways (20). Recently, the term "spread through air spaces" (STAS) has been introduced (21), but this describes an observation under the microscope immediately adjacent to the tumor, which is not indicated in our these two cases. Theoretically, the growth of non-invasive cells of lepidic adenocarcinomas can only through air space. "Aerogenous" dissemination maybe the unique pattern of its metastasis in the patients of this report. But it is different type from reported STAS. Dr. Detterbeck also mentioned the longitudinal study of serial biopsies in several patients published in *Thorax* 2014 by Pipinikas *et al.* (17). This special study suggests that "migration" through the respiratory epithelium can occur. But the process happened slowly and is not necessarily with ominous clinical impact. So it appears that the presence of genetically similar adenocarcinoma lesions in our study also may be the same phenomenon. "Migration" through the air space might be a specific way in the growth of atypical adenomatous hyperplasia (AAH) and adenocarcinoma in situ (AIS) from the very beginning, then to invasive tumors. And this process may be a fundamentally different way than what is traditionally considered. It is inappropriate to conclude that GGO did STAS from our study. Our observations only highlighted this unexpected pattern of spreading as case report. What is more, it is unknown as this time how often this happens.

In conclusion, genetically our study provided first piece of evidence, to the best of our knowledge, GGOs can metastasize, and metastatic lung cancer lesions could still be GGOs. It is welcomed to view our findings as "an interesting piece of a jigsaw puzzle, but one that I cannot yet connect sufficiently to other pieces to allow the image depicted by the entirety of the puzzle to emerge".

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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