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Title: The diagnostic puzzle of ALK rearrangement in lung cancer. A novel intron related abnormality

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Body: Introduction: The echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) gene fusion occurs in 2%-7% of non–small-cell lung cancer (NSCLC) and is typically identified by fluorescent in situ hybridization (FISH). Patient/Methods: We present two patients with NSCLC who carried unique, previously unpublished ALK rearrangement. Both were presented as advanced adenocarcinomas of the lung, who were wild type for EGFR and ALK rearrangement. Thanks to a high clinical suspicious for gene abnormality, further study was performed including comprehen-sive genomic profiling using a next-generation sequenc-ing (NGS) assay and ALK protein expression through IHC. Results: In both cases, we noticed high expression of the ALK protein. NGS analysis of genomic DNA revealed a complex rear-rangement of ALK, involving breakpoints in at least five dif-ferent genomic loci without a clear fusion product. The cDNA sequence showed that the expressed product of the complex rearrange-ment was the canonical EML4-ALK fusion gene. We hypothesized that at the genomic level the fused EML4 and ALK genes were sepa-rated by other small genomic shards. Based on these results, crizotinib was begun. The first patient showed an immediate benefit and is still a complete responder for 16 months. The other patient died before he was treated. Conclusions: This is the first report associated intron abnormality with ALK rearrangement abnormality. Further, we provide a tremendous clinical benefit from ALK related therapy that turned a metastatic patient to a complete responder. We recommend performing advanced molecular analysis through crossing technologies in any all patients.