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Non-Small Cell Lung Cancer in a Very Young Woman: A Case Report and Critical Review of the Literature

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Data Interpretation D
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Patient: Female, 19
Final Diagnosis: Lung adenocarcinoma
Symptoms: Chest pain
Medication: —
Clinical Procedure: Ct scan and pet-ct
Specialty: Oncology

Objective: Unusual clinical course

Background: Lung cancer in young patients is quite uncommon; clinical presentation and outcome in this population compared to the older group are not yet well defined and data about this setting are mostly single-institutional retrospective analyses.

Case Report: We report here a case of a very young woman with diagnosis of early-stage lung adenocarcinoma harboring *EML4-ALK* rearrangement; she underwent radical surgery and adjuvant chemotherapy according to the pathologic stage. Potential risk factors for lung cancer in our patient are discussed and clinico-pathologic features and outcomes of lung cancer in the young population compared to the elderly are reviewed through discussing studies with sample sizes larger than 100 patients.

Conclusions: A wide clinical overview should be performed when lung cancer is diagnosed in a young patient. Large-population studies are required to define the molecular signature and clinical behavior of lung cancer in young patients.

MeSH Keywords: Lung Neoplasms • Patient Outcome Assessment • Risk Factors • Young Adult

Abbreviations: **SEER** – Surveillance, Epidemiology, and End Results Program; **LC** – lung cancer; **CT** – computed tomography; **PET/CT** –positron emission tomography/computerized tomography; **VATS** – video-assisted thoracic surgery; **FISH** –fluorescent *in situ* hybridization; **ECOG** –eastern cooperative oncology group; **GGT** – gamma-glutamyl-transpeptidase; **CMV** – cytomegalovirus; **Ig** – immunoglobulin; **EBV** – Epstein-Barr virus; **SLE** –systemic lupus erythematosus; **HIV** – Human Immunodeficiency Virus; **HPV** – Human papilloma virus

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Background

According to the Surveillance, Epidemiology, and End Results Program (SEER) registry based on 2007–2011 new cases, lung cancer (LC) is more frequently diagnosed among people aged 65–74 with only 1.6% of all cases occurring in patients younger than 45 years [1]. Most published data about LC in young populations are single-institutional retrospective analyses and few report on very young patients specifically. Previous data suggest that LC in young adults may be an entity with distinct characteristics compared to LC in older patients; however, data are not always consistent among all series [2–11]. In addition, age limits ranging from 40 to 50 years have been variably chosen by different authors to define younger cohorts of patients. We report a case of a young woman with early-stage *EML4-ALK* rearranged lung adenocarcinoma who underwent surgery followed by adjuvant chemotherapy. We also consider possible susceptibility factors for LC in our patient and review the majority of clinical studies with a sample size larger than 100 patients, in order to highlight and discuss LC patterns in young versus old patients [2–11].

Case Report

In January 2014, a 19-year-old white, never-smoker woman experienced chest pain; a chest X-ray and a computed tomography (CT)-scan showed a cavitating right lung lesion in the upper lobe without enlargement of mediastinal lymph nodes (Figure 1A). A bronchoscopy was performed and the evaluation of cell block prepared from bronchial brushings led to the diagnosis of adenocarcinoma. A positron emission tomography/computerized tomography (PET/CT) scan excluded additional disease localizations (Figure 1B). In March 2014 the patient underwent right upper lobectomy with systematic lymphadenectomy by video-assisted thoracic surgery (VATS); a diagnosis of primary pulmonary adenocarcinoma with papillary predominant pattern was made. Immunohistochemistry

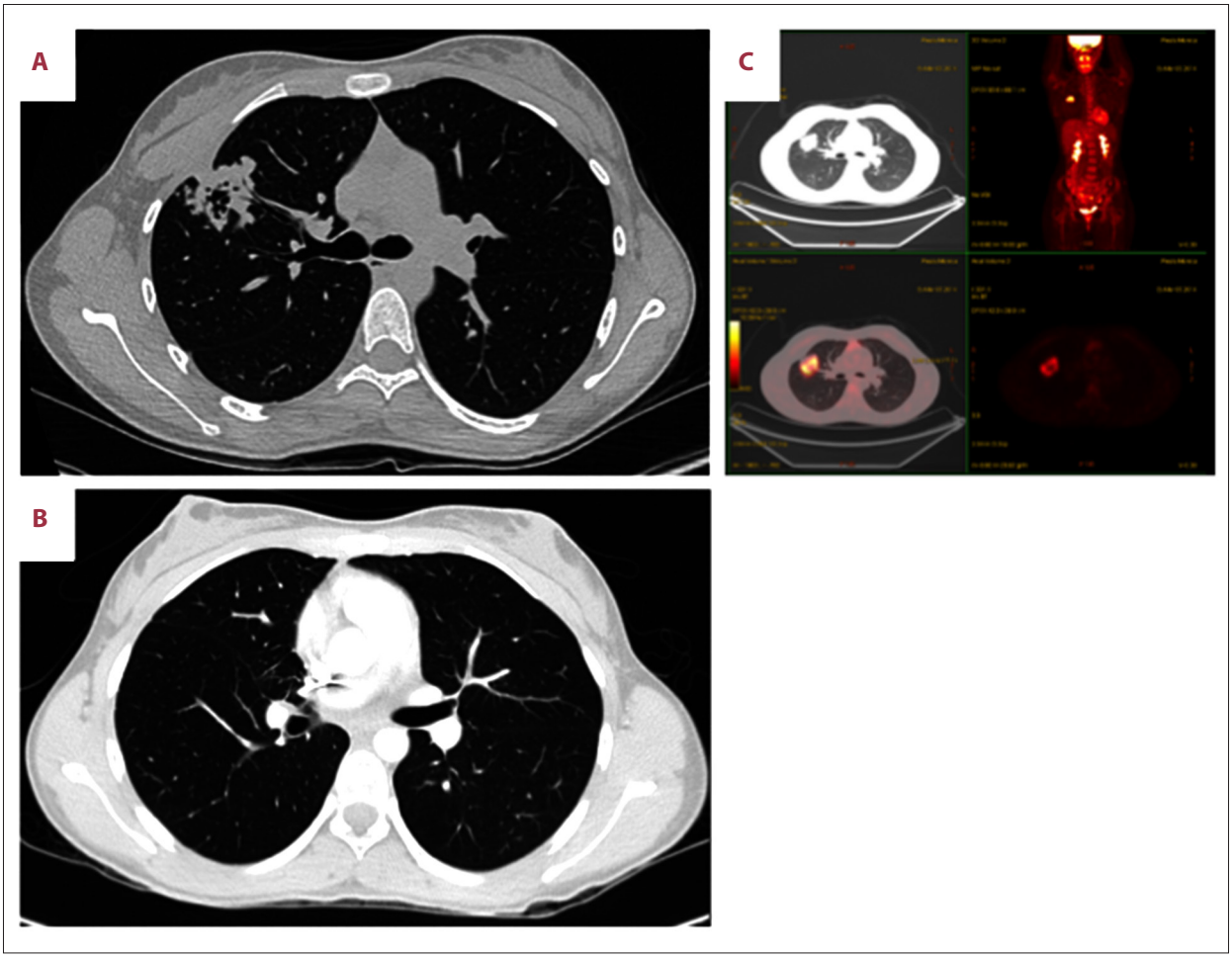

Figure 1. Computed tomography (CT) scan at diagnosis and positron emission tomography and CT-scan (PET/CT) at diagnosis, before surgery (**A, B**). CT scan after surgery at last follow-up visit (**C**).

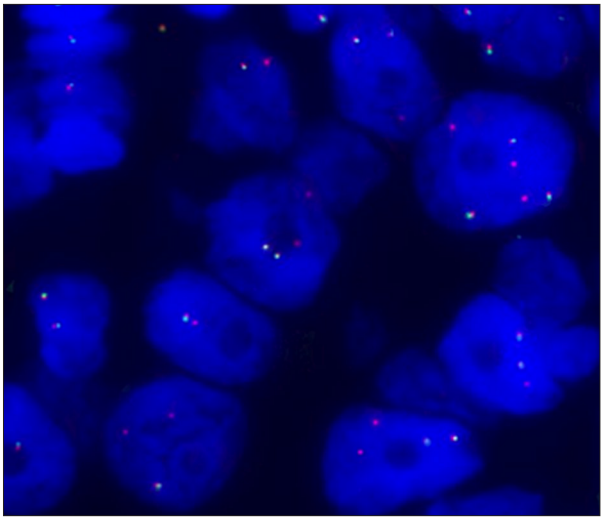

Figure 2. FISH analysis was performed with ALK dual-color break-apart probe labelled with SpectrumOrange (3'end) and SpectrumGreen (5'end) (Abbott Molecular). The predominant ALK-positive FISH pattern observed in the sample was isolated red signal.

showed that tumor cells were positive for TTF-1 and negative for p63; Ki67 was 70%. Molecular analysis showed no *EGFR*, *KRAS*, and *BRAF* gene mutations by Sanger's direct sequencing, whereas fluorescent *in situ* hybridization (FISH) showed the presence of *EML4-ALK* rearrangement in 57% of cells (Figure 2). The patient was then referred to our Institution in April 2014. Clinical examination showed Eastern Cooperative Oncology Group (ECOG) performance status 0, and no additional findings. As previous medical history, the patient referred a general discomfort occurring between May and October 2013, characterized by nausea, vomiting, diarrhea, and skin rash. Blood test results are reported in Table 1. In November 2013, the patient underwent an esophagogastroduodenoscopy with multiple biopsies, leading to the diagnosis of celiac disease. A gluten-free diet induced symptoms regression. The cancer family history revealed that the patient's father died of renal cell carcinoma in 2007. A genetic test on a blood sample did not show TP53 mutations and the constitutional karyotype was normal. According to the pathologic stage (pT2a N1, stage IIA), she received adjuvant chemotherapy with 4 cycles of cisplatin-pemetrexed from May to July 2014. Before starting chemotherapy, the patient underwent ovarian tissue cryopreservation and gonadotropin-releasing hormone analogue was administered during the adjuvant treatment. Because of persistence of elevated gamma-glutamyl-transpeptidase (GGT) and transaminases before and during chemotherapy, the patient had a specialist opinion, which resulted in the diagnosis of autoimmune hepatitis. Currently, the patient remains on oncological and hepatologic follow-up visits. At the last follow-up visit, in February 2015, a CT-scan showed no disease recurrence (Figure 1C).

Discussion

Occurrence of LC in young adults is quite uncommon and is characterized by peculiar epidemiological, clinical, and prognostic features. To date, the pathogenesis of this disease in young people is still very unclear. None of the known risk factors for LC could explain the early onset of the malignancy and no specific genomic alteration has been detected in this subgroup of patients.

According to the SEER registry, the proportion of African-Americans, Asian, and Pacific Islanders was higher among younger than older patients [1]. This epidemiologic discrepancy may be due to differences in carcinogens exposure or to biologic differences such as inefficient cell cycle arrest and DNA damage accumulation or cytochrome polymorphisms [9,12,13]. Regarding the clinico-pathologic features of LC in the young population, most retrospective series with sample sizes of more than 100 patients (Table 2) reported a higher proportion of women and adenocarcinoma in younger groups compared to older patients [3,4,6–11], but some cases of very young patients with squamous cell LC have also been reported in recent years [14–16]. Data on the proportion of asymptomatic patients at diagnosis in young and old groups are discordant. However, chest pain is definitively the most frequent symptom of younger patients in comparative analysis [6,8], such as in our patient. Finally, lower occurrence of early-stage disease in young people, described in most of the retrospective series, could be due to more aggressive disease or a delayed diagnosis due to a low degree of suspicion of cancer in young patients [4,9–11].

Our patient's tumor sample tested positive for *EML4-ALK* rearrangement. To date, only a few studies have investigated molecular alterations in younger patients, with controversial results. Higher frequency of *EML4-ALK* rearrangement (11.6%) and *EGFR* mutation (20%) were shown in 53 non-small cell LC patients ≤50 years old compared with patients of all ages [17]. In contrast, Ye et al. showed no difference in terms of oncogenic mutations (P=0.396), but a higher prevalence of TP53 mutations (P<0.001) in 36 resected lung adenocarcinoma from patients younger than 40 years compared to their older counterparts [18]; similarly, Kim et al. did not find a statistically significant difference in *EGFR* and *EML4-ALK* status between young and old patients [19]. Further investigation is needed to address the issue of genetic derangements in young patients with LC.

Risk factors for the onset of LC specifically in young adults are still unknown. The increased frequency of adenocarcinoma and the long latency time between smoking exposure and cancer appearance suggest that LC among young people does not require as much carcinogen exposure, but rather genetic

Table 1. Significant selection of blood tests performed before diagnosis of lung cancer.

Blood test	Result	Normal values
Alkaline Phosphatase (ALP)	95	42–98 (U/L)
Lactate Dehydrogenase (LDH)	175	135–214 (U/L)
Aspartate Transaminase (AST)	**215**	10–35 (U/L)
Alanine Transaminase (ALT)	**197**	7–35 (U/L)
Gamma-glutamyl transferase (GGT)	**470**	3–45 (U/L)
Gamma Globulins	**29.6**	11–20 (%)
Immunoglobulin (Ig) G	**288**	65–165 (ug/dL)
Anti-endomysial IgM	**Positive**	Negative
Anti-transglutaminase IgA	**17.3**	<4 (U/mL)
Anti-Nucleus Antibodies (ANA)	**Positive**	Negative
Anti-HBc IgM	Negative	Negative
Anti-HBc	Negative	Negative
Anti-HCV	Negative	Negative
Anti-HBsAg	**56**	Negative <10 UI/L, positive ≥10 UI/L
HBsAg	Negative	Negative
Anti-Cytomegalovirus IgG	**Positive**	Negative
Epstein-Barr Virus (EBV) Viral Capside Antigen (VCA) Ig G	**Positive**	Negative
EBV VCA Ig M	**Positive**	Negative
EBV Nuclear Antigen (EBNA) antibodies	**Positive**	Negative
Anti-Extractable Nuclear Antigens (ENA) antibodies	Negative	Negative
anti-Liver Kidney Microsomal (LKM) antibodies	Negative	Negative
Anti-Smooth Muscle Antibodies (ASMA)	Negative	Negative
Anti-Mithocondrial Antibodies (AMA)	Negative	Negative
Soluble Liver Antigen (SLA) antibodies	Negative	Negative
Anti-Neutrophil Cytoplasmic Antibodies (ANCA)	Negative	Negative
Anti-Saccharomyces Cerevisiae Antibodies (ASCA)	Negative	Negative
CEA	3.9	0.0–5.0 (ug/L)
CYFRA 21.1	1.2	0.0–3.3 (ug/L)

derangements. However, the smoking status is similar between younger and older patients in a few series collecting these data, with approximately 75–95% of young patients reporting smoking sometime. Whether the number of cigarettes smoked per day or the age at which smoking began lead to an early onset of LC is still unclear. These patients might have genetic susceptibility to develop LC or inherited sensitivity to smoking-related carcinogenesis. Recently, case-control studies have showed that gene mutations or polymorphisms involving xenobiotic metabolizing enzymes and DNA repair pathways are associated with increased risk of early-onset LC [20–23].

Our patient was a never-smoker female, and she did not report previous exposure to carcinogens; thus, when we investigated possible risk factors for LC, we focused on genetic, immunological, and/or infective predisposition. The hypothesis of

Table 2. Studies comparing young lung cancer patients to older patients with sample size of more of 100 patients: data about clinico-pathologic features.

	N (% of total)	Country, Year	Age cut-off	Smoking status*			Cancer cases in family			% of females			Histological type			Stage		
				Young (%)	Old (%)	P	Young (%)	Old (%)	P	Young (%)	Old (%)	P	Young (%)	Old (%)	P	Young (%)	Old (%)	P
Roviaro, 1985 [2]	155 (10%)	Italy, 1967–1980	<45 years	Smokers 93%	NA	NA	NA			8%	NR	NS	AC 18% SQ 64%	NR	NS	Stage I–III 92% Stage IV 8%	Stage I–III 96% Stage IV 4%	NS
McDuffie, 1989 [3]	187 (7%)	Saskatchewan (CA), 1979–1986	≤50 years	Smokers 85%	Smokers 78%	NS	One first-degree relative with LC			46%	22%	***P*<0.001**	NR		***P*<0.005**		NA	
							7.5%	6%	NS									
Ramalingam, 1998 [4]	2804 (9%)	Metropolitan Detroit SEER registry, 1973–1992	<50 years		NA		NA			40%	31%	***P*<0.001**	AC 46% SQ 27%	AC 34% SQ 38%	***P*<0.001**	Local 19% Distant 53%	Local 25% Distant 49%	***P*<0.001**
Kreuzer, 1998 [5]	251	Germany, 1990–1996	≤45 years	Smokers 95%	Smokers 94%	NA	One first-degree relative with LC			27%	15%	NA	AC 42% SQ 24%	AC 31% SQ 39%	***P*=0.3**	NA	NA	NA
							10%	7%	NA									
Kuo, 2000 [6]	127 (2%)	Taiwan, 1987–1996	<40 years		NA		NA			52%	NR	***P*<0.001**	AC 61% SQ 21%	NR	***P*=0.0004**	Stage I 9% Stage IV 47%	Stage I 15% Stage IV 40%	NS
Radzikowska, 2001 [7]	757 (14%)	Poland, 1995	≤50 years	Smokers 76%	Smokers 77%	P=0.349	Cancer cases in family (mother and father)			24%	12%	***P*<0.001**	AC 13% SQ 35%	AC 8% SQ 42%	***P*<0.001**	Stage I 24% Stage IV 19%	Stage I 23% Stage IV 15%	*P*=0.059
							***P*<0.001**											
Mauri, 2006 [8]	115 (6%)	Greece, 1989–2004	≤45 years	Smokers 77%	Smokers 75%	P=0.326	NA			18%	12%	*P*=0.071	AC 49% SQ 24%	AC 43% SQ 37%	***P*=0.004**	Stage IV 12%	Stage IV 22%	***P*=0.016**
Subramanian, 2010 [9]	2775 (1%)	SEER registry, 1988–2003	≤40 years		NA		NA			49%	42%	***P*<0.0001**	AC 58% SQ 13%	AC 45% SQ 26%	***P*<0.0001**	Stage I 12% Stage IV 57%	Stage I 21% Stage IV 43%	***P*<0.0001**
Inoue, 2014 [10]	704 (6%)	Japan, 2004	≤50 years	Smokers 47%	Smokers 57%	P<0.001	NA			47%	37%	***P*<0.001**	AC 79% SQ 7%	AC 67% SQ 23%	***P*<0.001**	Stage I 64% Stage III–IV 24%	Stage I 65% Stage III–IV 20%	***P*<0.001**
Rich, 2015 [11]	651 (0.4%)	English National Lung Cancer Audit, 2004–2011	18–39 years		NA		NA			44%	43%	NR	AC 48% SQ 13%	AC 33% SQ 33%	NR	Stage I 9% Stage IIIB–IV 71%	Stage I 14% Stage IIIB–IV 61%	NR

* Smokers (current smokers and exsmokers) *versus* Nonsmokers. NA – not assessed; NS ,– not significant; NR – not reported; LC – lung cancer; SEER – surveillance, epidemiology, and end results; AC – adenocarcinoma; SQ – squamous cell carcinoma

Table 3. Studies comparing young lung cancer patients to older patients with sample size of more of 100 patients: data about patients' outcome.

	1-year OS rate			5-year OS rate			OS			
	Young	Old	P	Young	Old	P	Young	Middle-age	Old	P
Roviaro, 1985 [2]		NA		21%	25%	NS			NA	
Ramalingam, 1998 [4]		NA		16%	13%	***P*<0.001**			NA	
Kuo, 2000 [6]		NA			NA		9 months	8 months	4 months	***P*<0.0001**
Radzikowska, 2001 [7]	33%	29%	***P*<0.049**		NA			NR		***P*=0.01107**
Mauri, 2006 [8]		NA			NA		12 months	NA	11.5 months	*P*=0.277
Subramanian, 2010 [9]		NA			NA		Younger patients had better stage-wise overall and disease-specific survival than older patients			***P*<0.0001**
Inoue, 2014 [10]		NA		79%	69%	***P*<0.001**			NA	
Rich, 2015 [11]		NA			NA		Young patients had a lower overall mortality than older patients (62% *vs.* 86%, respectively)			***P*<0.001**

OS – overall survival; NA – not assessed; NS – not significant; NR – not reported.

a genetic component in the early onset of LC is also supported by a few series showing an increased family history among young patients. In a case-control study, the authors demonstrated the greatest contribution to LC risk (7-fold increase) among 40- to 59-year-old non-smoker subjects with a first-degree relative affected by LC [24]. Our patient did not report family history of LC among her first-degree relatives. Her father died because of a kidney cancer, which is not included in any genetic syndrome involving LC; moreover, germ-line mutations of TP53 gene or constitutional karyotype alterations were not observed. Hereditary LC syndromes are rare, and, while germline *EGFR* T790M mutation has been reported as a predisposing genetic feature, especially in non-smoker patients [25], no evidence of germline *EML4-ALK* rearrangement has been reported in LC.

The medical history of the patient included the diagnosis of celiac disease, which is associated with an increased risk of lymphoma. In a study from a large Swedish cohort, the authors found a neutral risk of LC in celiac disease, with a hazard ratio of 1.00 beyond the first year of follow-up after celiac diagnosis [26]. More recently, a large-population cohort study in Finland showed a decreased risk of LC among 32 439 celiac patients [27].

Additional significant findings in our case were the recent diagnosis of autoimmune hepatitis, anti-cytomegalovirus (CMV), immunoglobulin (Ig) G, and anti-Epstein-Barr virus (EBV) IgG and IgM positivity. Subsequent examinations excluded the positivity of CMV and EBV DNA and of all hepatitis viruses. The association between solid cancer and autoimmune systemic disease is uncommon and especially involves scleroderma and LC [28], even though increased risk for LC has also been reported in systemic lupus erythematosus (SLE) patients [29]. In a recent paper, a 4-fold risk of LC in patients with systemic sclerosis, discoid lupus erythematosus, and polymyositis/dermatomyositis has been described [30]. However, there are no data about a possible link between autoimmune hepatitis and risk of LC. Similarly, EBV and CMV infections seem to have a role in the pathogenesis of solid tumors, such as lymphoepithelioma-like carcinoma and glioblastoma, respectively, but no involvement in LC risk has been reported. Indeed, microRNA studies in LC did not support any role of EBV in LC [31]. To date, the only virus infections associated with LC are human immunodeficiency virus (HIV) and human papilloma virus (HPV) infections [32,33]. Thus, we have no data to support the hypothesis that LC risk in our patient had a genetic, immunological, or infective basis.

Data regarding clinical outcome of young LC patients have been presented in only a few retrospective studies [2,4,6–11] (Table 3). According to Roviaro GC et al., no significant statistical differences were observed in terms of survival between patients younger or older than 45 years, in the whole population and according to type of treatment or disease [2]. This was also confirmed by another series in which the majority of examined patients were included in clinical trials, thus making the 2 groups well balanced in comorbidity patterns and treatment modalities [8]. On the other hand, other studies showed a longer survival in the young group, despite the higher frequency of advanced disease. This finding could be explained by the higher chance of receiving more aggressive treatments, including multimodality treatments and further lines of chemotherapy, due to the lower prevalence of comorbidities [4,6,7,9–11].

In case of disease relapse, our patient could benefit from a first-generation *ALK* inhibitor, which has demonstrated remarkable clinical outcomes including better response rate and prolonged survival compared to standard chemotherapy [34,35]. However, despite an initial improvement, *ALK*-positive tumors inevitably develop several resistance mechanisms to the targeted drug, resulting in progression of the disease. Other strategies, including the development of new-generation *ALK* inhibitors, are currently under clinical evaluation to overcome the acquired resistance in these patients [36].

Conclusions

Despite a comprehensive review of the patient's medical and family history, we did not identify any underlying risk factor for LC. Larger prospective studies are needed to define the molecular signature and clinical behavior of LC in young patients. To collect evidence of no-smoking related pathways involved in cancer risk, a wide clinical overview should be performed when LC diagnosis occurs in a young patient. Given the rarity of the disease in this setting, only an international multicenter study could address this issue.

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